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CONTENTS

Diagnostic accuracy for coronary artery disease by computed tomography angiography as compared to conventional invasive angiography..... 1
Dr. Forat Tariq Youash
Dr. Mohammed Ali Khalaf

Two-Dimensional Speckle-Tracking Echocardiography to Monitor Left Ventricular Function After Percutaneous Coronary Intervention **21**
Dr. Khalil S. Ahmed

Generalized Anxiety Disorder among Adult patients attending psychiatric clinic at Baghdad Teaching Hospital **41**
Dr. Hamid Ahmed Wahbie
Dr. Abbas Al_Rubayee

Evaluation of Maternal Serum Homocysteine in Pre eclampsia **62**
Dr. Maha Azeez Tawfeeq
Dr. Khalidah Amin

The Relation between Chronic Viral Hepatitis B Infection and Helicobacter Pylori Infection..... ..... **75**
Dr. Saman Khazal Jafar
Dr. Makwan Mohammed Abdulkareem
Dr. Mohammed Omer Mohammed

Correlation between HbA1c and lipid profile in patients with Type2 diabetes mellitus **101**
Dr Abdulwahed Hasan Muhammed

Spontaneous Correction of Extreme Degree Femur Ante –Version in Developmental Dysplasia of the Hip..... ..... **108**
Dr. Yousif Rashid Mohammed

Does mitomycin-C and triamcinolone injection therapy during optical urethrotomy able to reduce the recurrence of urethral stricture? A comparison study..... **118**
Dr. Ahmed Mahmood Hussein
Dr. Sarkawt Khursheed Raheem
Dr. Firas Dahham Ammash

A Double Cerclage and Tension band Wiring Technique Fixation for Comminuted Patellar Fractures **131**
Dr. Yousif Rashid Mohammed

ULTRASOUND MEASUREMENT OF OPTIC NERVE SHEATH DIAMETER IN A SAMPLE OF IRAQI ADULTS **141**
Dr. Mustafa Yashar Ali
Dr. Suzan A.M. Abdul Kareem

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Original article

Diagnostic accuracy for coronary artery disease by computed tomography angiography as compared to conventional invasive angiography

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Abstract:

- ***Background***: Emerging as a major cause of death and disability in the developing countries is coronary artery disease (CAD). Traditional coronary angiography has traditionally been the preferred diagnostic procedure for CAD. Non-invasive evaluation of coronary artery disease (CAD) using computed tomography (CT) coronary angiography shows promise. This observational study's goal is to assess the relative efficacy of noninvasive multi-section computed tomography (MSCT) coronary angiography vs invasive selective coronary angiography in detecting coronary stenosis.
- ***Method and patient:*** This observational study carried out in the Azadi teaching Hospital/Kirkuk between November 2021 to March 2022. Patients who suspected to have coronary artery disease underwent both CTCA and invasive coronary angiography in different centers in our country comparing and analyzing their results.
- ***Result:*** In total, 92 participants were enrolled in the trial. Patients had a mean age of 57.207.3 years, and men made up the vast majority of those who appeared (67.3 percent). Chest pain was the most common presenting complaint (94 percent). Patients exhibited a prevalence of 84% for HTN, 55% for hyperlipidaemia, 58% for diabetes, and 4% for ischemic heart disease. In addition, 50% of the patients are either current or former smokers. Half of the patients received 64-slice CT scans, nearly half had 128-slice scans, and 3.2% got 256-slice scans. CCTA's sensitivity was 100%, and its specificity was 66.7%.

Positive predictive value for CCTA was 98.8 percent (meaning it correctly identified positive cases in 98.8 percent of patients) and negative predictive value was 100 percent, for a total diagnostic accuracy of 98.9 percent (which mean CCTA can exclude all negative cases and did not miss any case). When looking at individual arteries, the LAD artery was shown to be the most accurate, while the LCX artery was the least accurate (95.6 percent and 78.2 percent respectively). In terms of sensitivity, LAD performed at a 99.1% rate, while LMS performed at a 0% rate (33.3 percent). RCA had the most specificity (95.2 percent), whereas LAD had the lowest (88.8 percent) (40 percent). In order to determine what factors, influence CCTA positivity, we performed a binary logistic regression analysis for positive CCTA (negative as reference) with all variables from the studies. The results showed that IHD, lesions in the LAD artery, lesions in the LCX artery, and CT slice thickness (128 and 256 slices) all have a negative effect on CCTA (p0.05).

- ***Conclusions:*** When compared to traditional angiography, multi-slice computed tomography has demonstrated superior sensitivity and specificity for the identification of coronary artery disease.
- **Keywords:** Coronary artery disease, Computed tomography, coronary angiography, Conventional coronary angiography.

INTRODUCTION

Emerging as a major cause of death and disability in the developing countries is coronary artery disease (CAD). Traditional coronary angiography has traditionally been the preferred diagnostic procedure for CAD [(1)]. In the context of catheter-based or surgical treatments, it offers superb resolution for seeing the coronary arteries. Mortality is a very rare complication of this procedure, but it relates to a number of other problems, both cardiac and otherwise [(2)].

Noninvasive evaluation of coronary artery disease (CAD) using computed tomography (CT) coronary angiography shows promise [(3)]. coronary artery disease is evaluated, and both qualitative and quantitative data on the presence and extent of non-obstructive atherosclerotic plaque in the arterial wall are provided. This suggests that CT angiography-based disease evaluation may yield more useful information for patients than does standard angiography. High diagnostic accuracy of CT coronary angiography has resulted from the development of multi-slice computed tomography (MSCT) technology, such as 64-slice, 128-slice, 256-slice, and now 320-slice MSCT [(4)].

With a negative predictive value constantly exceeding 90%, it has been shown to reliably exclude patients who have severe CAD, whereby coronary luminal stenosis is defined as 50%.

Therefore, the purpose of this study is to compare the diagnostic yield and accuracy of coronary CT angiography (CCTA) with invasive coronary angiography (ICA) in patients referred for invasive coronary angiography due to clinical concern for coronary artery disease (CAD). [5, 6].

CAD, or coronary artery disease: Atherosclerosis's pathophysiology is still poorly understood. Atherosclerosis likely has a complex pathophysiology due to the interaction of environmental and genetic variables. Some 'new' risk factors and as-yet-unrecognized factors may be as important as the 'traditional' ones as HTN, dyslipidemia, DM, and smoking. The high rate of CAD in Iraq may be a result of any one of these variables acting alone or in various combinations within a genetically susceptible population [1,7,8]. Standard invasive angiography (CIA) has been the gold standard for verifying the diagnosis of CAD for several decades. As part of coronary angiography, a catheter is inserted into an artery in the groin, arm, or shoulder and guided to the heart. Digital X-ray images are taken as iodinated contrast dye is injected directly into the coronary arteries [9 – 11].

Figure 1. Atherosclerosis of the Coronary Arteries. Coronary angiogram and cardiac catheterization demonstrating significant left anterior descending (LAD) stenosis in the left panel. As can be seen in the right panel, a stent was placed in the left anterior descending coronary artery to treat this lesion [13]

The diagnostic accuracy of invasive coronary angiography has various drawbacks. Visual estimations of stenosis severity are common, but they have their limitations due to inter-observer variability that can vary from 30 to 60 percent. As the stenosis areas are reported as a percentage of luminal diameter in comparison with surrounding normal coronary segments, and, in diffuse disease, no such segments are detected, the presence of diffuse disease may also contribute to underestimating of stenosis [12-14].

The fractional flow reserve computed tomography (FFRCT) approach has recently emerged as a non-invasive method for assessing the severity of epicardial coronary narrowing and the physiological consequences of this narrowing [15,16].

To get around the drawbacks of CIA, multi-slice computed tomography angiography (CTA) has been recommended in recent years as an alternative method of diagnosing coronary blockages. Recent advances in technology with many detectors have greatly enhanced spatial and temporal resolutions of pictures, making CTA the focus of doctors' attention [17] This observational study's goal is to assess the relative efficacy of noninvasive multi-section computed tomography (MSCT) coronary angiography vs invasive selective coronary angiography in detecting coronary stenosis [22], This observational study's goal is to assess the relative efficacy of noninvasive multi-section computed tomography (MSCT) coronary angiography vs invasive selective coronary angiography in detecting coronary stenosis [18-21].

PATIENT and METHOD

This research was conducted from November 2021 to March 2022 at the Azadi Teaching Hospital in Kirkuk. All patients who fulfilled the following inclusion criteria were included in the study: Patient must be 18 years or older. Suspect angina related to coronary heart disease because of chest pain. Individuals who are at a moderate risk for developing coronary artery disease but not at a high risk. Criteria for exclusion: Those who are unable or unwilling to undergo CTCA. People who have developed an episode of acute coronary syndrome (up to 100 days previously). A glomerular filtration rate of 30 ml/min or below indicates chronic kidney disease. Patients who are pregnant women. Systemic comorbidity individuals, such as those with severe COPD, who cannot hold their breath while imaging. Direct questionnaire interviews are conducted with each respondent to acquire the following data: In the first section, you'll be asked questions about your demographics and your health. Give your full name, date of birth, gender, job title, and a brief introduction. Examining the presence of many disorders: ischemic heart disease, diabetes, high cholesterol, high blood pressure, high blood sugar, high body mass index, and a normal electrocardiogram all point to a healthy lifestyle.

Part 2 involves comparing and analyzing the outcomes of CTCA and invasive coronary angiography in patients who gave their informed consent for both procedures. Multiple observers, each of whom was uninformed of the multi-slice CT results, classified coronary lesions as either single-vessel, double-vessel, or triple-vessel disease. To be compared with invasive angiography, lesions of any size are included. According to the degree to which an artery has been blocked, lesions are categorized.

The majority of our patients' CTCA and CIA were performed in the city of Kirkuk in northern Iraq, and the interval between their tests ranged from a few weeks to three months. Regarding the ethical considerations, Approval was taken from Internal Medicine Scientific Committee of Iraqi Board, an agreement for research was taken from hospitals' authorities, written informed

consent was taken from each patient. The statistical package for social sciences (SPSS) software version 23 had been used for data entry and analysis. In the descriptive statistics for socio-demographic characteristics, the means, standard deviations, min, max values were used for continuous data. Numbers and percentage values were used for countable data. In analyzing the differences between the groups, chi square and T test were used. Binary logistic analysis was used to evaluate the possible factors associated with positive CCTA. P<0.05 was used as the threshold for statistical significance.

RESULTS

There were 92 patients included in this study.

Demographic characteristics: The mean age of patients was 57.2 ± 7.3 years (range 44 – 75 years).

Table 1. Descriptive statistics of age

	Mean	SD	Minimum	Maximum
Age	57.2	7.3	44	75

Majority of presented patients were males (67.3%) (Figure 3.1).

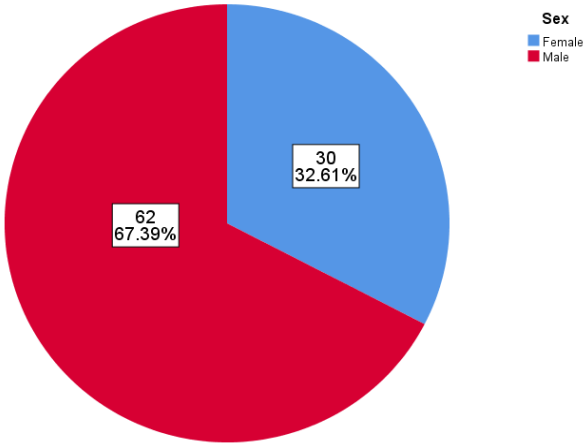

Figure 1. Gender distribution across patients

The majority of patients were presented with chest pain (94%). There were 85%, 55%, 58%, and 4% of patients had HTN, hyperlipidemia, DM, and IHD respectively. Also, 50% of patients are currently smokers or ex-smokers (Table 2).

Table 2. Demographic characteristics of patients

		Count	N %
Chest Pain	No	5	5.4%
	Yes	87	94.6%
Dyspnea	No	45	48.9%
	Yes	47	51.1%
Palpitation	No	54	58.7%
	Yes	38	41.3%
Occupation	Employee	23	25.0%
	Free worker	30	32.6%
	Housewife	27	29.3%
	Retired	10	10.9%
	Teacher	2	2.2%
HTN	No	13	14.1%
	Yes	79	85.9%
Hyperlipidemia	No	41	44.6%
	Yes	51	55.4%
DM	No	38	41.3%
	Yes	54	58.7%
IHD	No	88	95.7%
	Yes	4	4.3%
Smoking	Yes	34	37%
	Ex smoke	12	13.0%
	No	46	50.0%

Regarding vital signs and BMI, the descriptive statistics are given in below table 3.

Table 3. Descriptive statistics of vital signs and BMI

	Mean	SD	Minimum	Maximum
SBP	138	13	110	170
DBP	82	11	60	100
HR	78	8	56	105
RR	14	1	10	16
BMI	27	3	23	36

Regarding the ECG changes, majority of patients presented with ST segment changes (75%) (Figure 2).

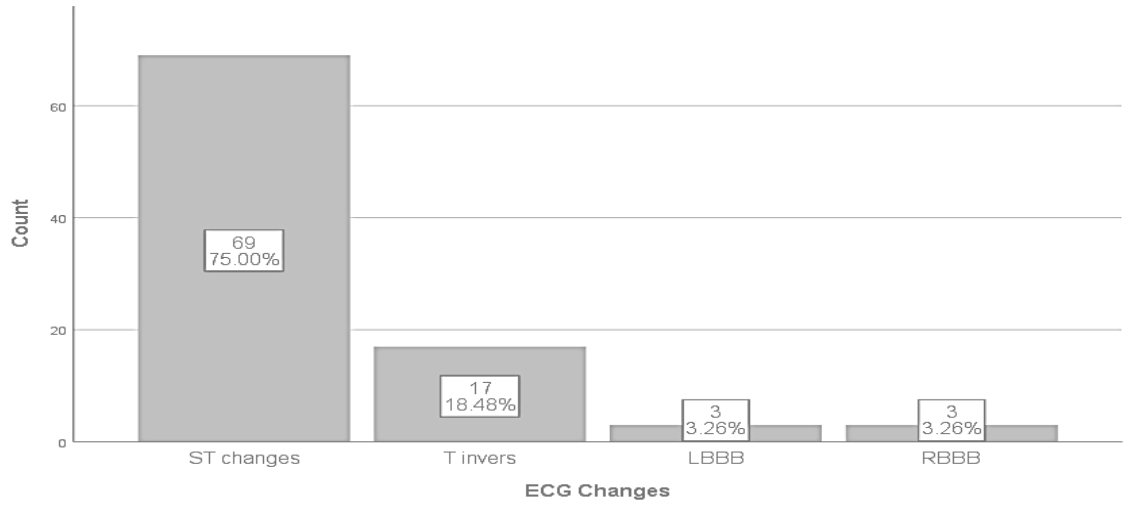

Figure 2. ECG changes across patients

Coronary CT angiography (CCTA): There were 50% of patients had 64-slice CT, 46.7% of patients had 128-slice CT, and 3.2% patients had 256-slice CT (Figure 3).

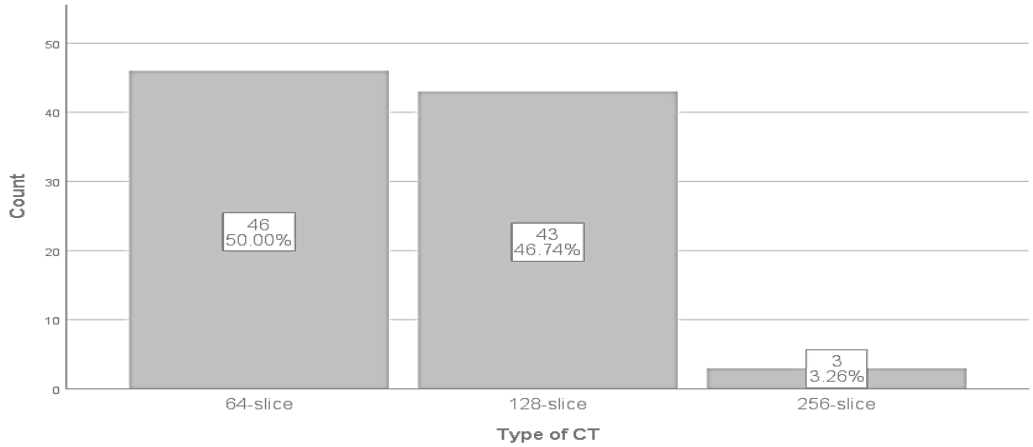

Figure 3. Type of CT performed.

The sensitivity of CCTA was 100% with specificity of 66.7%. The diagnostic accuracy of CCTA was 98.9% with PPV of 98.8% (which mean CCTA can identify positive cases in 98.8% of patients) and NPV of 100% (which mean CCTA can exclude all negative cases and did not miss any case).

Table 4. Comparison between CCTA and Conventional invasive angiography for diagnosis of CAD

		Conventional invasive angiography		Total
		Positive	Negative	
CT	Positive	89 (100%)	1 (33.3%)	90 (97.8%)
	Negative	0	2 (66.7%)	2 (2.2%)
Total		89 (100%)	3 (100%)	92 (100%)

P=0.0001

Table 5. Diagnostic accuracy of CCTA based on conventional invasive angiography

Test	Value
Sensitivity	100%
Specificity	66.7%
Positive predictive value	98.8%
Negative predictive value	100%
Accuracy	98.9%

For specific artery accuracy, the highest accuracy was observed for LAD artery while LCX artery showed lowest accuracy (95.6% and 78.2% respectively). The highest sensitivity was observed with LAD (98.9%) while LMS showed lowest sensitivity (33.3%). The specificity was at its highest level with RCA (95.2%) while lowest specificity was observed with LAD (40%).

Table 6. Comparison between CCTA and conventional invasive angiography for diagnosis of CAD per location

Location	CCTA		Angiography		P value
	Positive	No lesion	Positive	No lesion	
LMS	10 (10.9%)	82 (89.1%)	3 (3.3%)	89 (96.7%)	0.2
LAD	89 (96.7%)	3 (3.3%)	87 (94.6%)	5 (5.4%)	0.001
RCA	42 (45.7%)	50 (54.3%)	50 (54.3%)	42 (45.7%)	0.001
LCX	60 (65.2%)	32 (34.8%)	54 (58.7%)	38 (41.3%)	0.001

Table 7. Diagnostic accuracy of CCTA based on conventional invasive angiography per location

Artery	Sensitivity	Specificity	PPV	NPV	Accuracy
LMS	33.3%	89.9%	90%	97.6%	88%
LAD	98.9%	40%	96.6%	66.7%	95.6%
RCA	80%	95.2%	95.2%	80%	86.9%
LCX	87%	65.8%	78.3%	78.1%	78.2%

Factors associated with CCTA positivity: By running binary logistic regression analysis for positive CCTA (negative as reference) with all studies variables to test the factors that impact CCTA positivity, the test showed that, IHD, lesion in LAD artery, lesion in LCX artery, and type of CT (128 and 256 slices) effect negatively CCTA ($p<0.05$) (Table 8).

Table 8. Factors associated with CCTA positivity

			Score	DF	P value
	Variables	Age	0.003	1	0.959
		Sex	0.989	1	0.320
		Occupation	6.133	4	0.189
		HTN	0.336	1	0.562
		Hyperlipidemia	1.644	1	0.200
		DM	1.439	1	0.230
		IHD	44.978	1	0.001
		Smoking	2.044	1	0.432
		SBP	0.628	1	0.428
		DBP	3.087	1	0.079
		HR	0.316	1	0.574
		RR	2.870	1	0.090
		BMI	1.307	1	0.253
		ECG Changes	0.681	3	0.878
		LMS	0.249	1	0.618
		LAD	60.652	1	0.001
		RCA	1.717	1	0.190
		LCX	3.833	1	0.050
		Type of CT	14.723	2	0.001
		Chest Pain	0.117	1	0.732
		Dyspnea	2.135	1	0.144
		Palpitation	1.439	1	0.230
	Overall Statistics		77.802	41	0.001

There was no significant association between the comorbidities and CT nor O2 saturation (P>0.05) (Table 9).

Table 9. Group Statistics comparison of BMI with CT and O2 saturation

	Variable	N	Mean	SD	P value
C.T scan	Hypertension	36	67.78	15.741	0.76
	No	64	66.80	15.207	
O2 sat.	Hypertension	36	83.92	5.674	0.71
	No	64	83.44	7.536	
C.T scan	DM	27	70.37	14.539	0.2
	No DM	73	65.96	15.538	
O2 sat.	DM	27	82.44	5.235	0.3
	No DM	73	84.04	7.404	
C.T scan	Others	10	63.00	18.439	0.36
	No comorbidities	90	67.61	14.995	
O2 sat.	Others	10	85.10	6.903	0.47

DISCUSSION

When it comes to visualizing coronary artery disease, CCTA is state-of-the-art. CCTA is useful for assessing heart chambers, valves, great vessels, pericardium, and surrounding tissues, even though coronary atherosclerosis is the primary cause for the burden of cardiovascular illnesses [(2)]. This study was created to evaluate CCTA's diagnostic performance specifically for coronary arteries.

Among all patients, there was a mean age of 57.2 7.3 years. This matched the results of a recent study by Mohammad et al. in Iraq, which found that CAD patients, on average, were 55 years old [(13)], Another study by Mohammad et al. found that patients with advanced CAD had a mean age of 63, thus ours is in line with that. 9 Additionally, Elliott et al. found that the average age of CAD patients was 55 in research conducted in the United Kingdom. These findings lend credence to the widely held belief that coronary artery disease is a leading cause of death and disability among adults [(56)].

Most patients in this study were male, which is consistent with a study conducted in Iraq by Mohammad et al. that found 62% of adults with CAD were male [(13)].

13 Elliott et al. conducted research in the UK and found that 58% of CAD patients were female. 9 Possible explanations for this discrepancy include varying sample sizes and underlying genetic variables [(9)].

The most common presenting complaint was chest pain (94 percent). Historically, coronary artery disease has been represented by angina, which is a pain in the sub-sternal region that is described as a squeezing or heavy feeling and that may radiate to the medial aspect of the left upper extremity, to the neck, or to the jaw, and that may be accompanied by nausea, vomiting, palpitations, diaphoresis, syncope, or even sudden death. Even if a patient presents with seemingly unrelated symptoms, doctors and other medical professionals should keep their guard up and treat them with caution [(52)].

Patient prevalence of hypertension, elevated cholesterol levels, diabetes mellitus, and ischemic heart disease was 84%, 55%, 58%, and 4%, respectively. The most common risk factor was found to be hypertension (55.3%), followed by dyslipidemia (42.7%), type 2 diabetes mellitus (29%), smoking (11%), and ex-smoking (22%). (9.3 percent). A possible explanation for the discrepancy could be because the two-research used different sized samples [(13)].

Carbon monoxide, tar, nitrosamines, polycyclic aromatic hydrocarbons, hydrogen cyanide, aldehydes, and heavy metals are only few of the thousands of toxic chemicals found in tobacco. Evidence from epidemiological and clinical investigations shows that cigarette smoking increases the risk of cardiovascular events in a dose- and time-dependent manner. Acute myocardial infarction occurred roughly ten years earlier in smokers [(53)].

CCTA's sensitivity was 100%, and its specificity was 66%. CCTA has a 98.9% sensitivity, a 98.8% specificity (meaning it can detect positive cases in 98.8% of patients), and a 100% NPV (meaning it can detect no false positives) (which mean CCTA can exclude all negative cases and did not miss any case). Similar results were found in another study by Joshi et al., which found a sensitivity and specificity of 100% (95 percent confidence interval [CI]: 39.76 percent -100 percent) and 91.30 percent (95 percent CI: 79.21 percent -97.58 percent) for CT angiography, respectively. CT angiography had a strong positive predictive value (50 percent; 95% CI: 15.70 percent to 84.30 percent) and a high negative predictive value (100 percent; 95% CI: 91.59 percent to 100 percent) in this group of patients [40,41].

In addition, Mannan et al. found that CCTA has a sensitivity of 83.8% for detecting stenosis, a specificity of 98.4%, and an accuracy of 96.5%; based on these results, the authors concluded that CCTA permits the identification of coronary stenosis with excellent accuracy and well correlation with conventional angiogram. Despite this, Mannan et al. relied on only 64 CCTA slices in their analysis [43,45,46], In addition, the positive CCTA was shown by Meinel et al. to have a positive predictive value of 83% for individuals with clinically significant CAD, 100% sensitivity, and 84% specificity [47,48].

The diagnostic accuracy of coronary computed tomography angiography for coronary artery disease (CAD) was also demonstrated by Nielsen et al. to be higher than that of standard exercise electrocardiography and single-photon emission computed tomography [47].

Wu et al. found that coronary CT coronary angiography (CTCA) was more sensitive than the ‘standard diagnostic technique' in identifying patients with angina owing to coronary heart disease while also being less expensive [48,49].

In addition, a recent Egyptian study by Abd Ella et al indicated that CTCA has a sensitivity, specificity, and accuracy of 97.1, 96.8, and 96.8 percent, respectively, when compared to traditional angiography for diagnosing severe stenosis in coronary arteries [36 ,37].

Based on 64-slice CT evaluations of 923 segments from 68 patients, Nikolaou et al. found a sensitivity of 82%, specificity of 91%, a positive predictive value of 72%, a negative predictive value of 97%, and an accuracy of 93%. On a sample of 113 patients, Kerl et al. found that 64-slice CT had a sensitivity of 90.5%, specificity of 98.4%, positive predictive value (PPV) of 85.5%, negative predictive value (NPV) of 99.0%, and accuracy of 97.7% [40].

Accuracy for individual arteries varied, with the LAD artery showing the most precision and the LCX artery the least (95.6 percent and 78.2 percent respectively). LAD demonstrated the most sensitivity (98.9%), whereas LMS had the lowest (33.3 percent). The RCA had the most specificity (95.2%), while the LAD had the lowest (40 percent). Similar findings were seen in a recent Egyptian study by Abd Ella et al., demonstrating varying sensitivity and specificity with respect to particular artery obstruction [54].

To further investigate the factors that influence CCTA positivity, we ran a binary logistic regression for positive CCTA (negative as reference) with all study variables. The results showed that IHD, LAD artery lesion, LCX artery lesion, and CT slice count (128 vs. 256) all have a negative effect on CCTA positivity. These factors may influence the outcomes; however, the size of the sample may be more influential [30.31].

In a study comparing CCTA and invasive coronary angiography, Knaapen concluded that CCTA was close but not close enough to replace invasive coronary angiography, but that over the past decade, noninvasive computed tomographic coronary angiography (CCTA) has emerged as a viable alternative to its invasive counterpart [53]. A negative CCTA of adequate quality virtually excludes out obstructive CAD and considerably minimizes unnecessary invasive treatments, which is especially important given the low yield of ICA for detecting CAD [52,53] However, CCTA is used more as a screening tool for ICA rather than as a replacement for it because of worse image quality due to reduced spatial and temporal resolution, motion and blooming artifacts, and the need for a low and steady heart rate for optimal image capture. Due to its low specificity and high false-positive rate, CCTA has always been its own downfall, and further diagnostic methods are warranted in the event of a positive scan. After a CCTA that is either inconclusive or positive, myocardial perfusion imaging has been recommended to boost specificity. However, this approach has been shown to contribute little to no value over CCTA alone to identify CAD, and instead just boosts specificity at the expense of sensitivity without significantly improving total diagnosis accuracy, and therefore may be regarded even un useful for clinical decision-making. Now that we're moving away from these hybrid or sequential imaging methodologies, we can put our energy into perfecting CCTA as a stand-alone diagnostic tool that can potentially replace ICA [50,53].

It's interesting to note that a March 2022 study by Li et al. found that CCTA's diagnostic performance changes depending on the level of experience of the reading physician. It has been demonstrated that as one's experience with CCTA grows, so does its diagnostic precision. Few patients had 256-slice CCTA, and the sample size was limited overall [54].

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Nil.

Conflicts of interest:

There are no conflicts of interest**.**

CONCLUSION

1. We found that CCTA has a sensitivity of 100% and a specificity of 66.7% in our investigation.
2. CCTA has a 98.9% sensitivity, a 98.8% specificity (meaning it can detect positive cases in 98.8% of patients), and a 100% NPV (meaning it can detect no false positives) (which mean CCTA can exclude all negative cases and did not miss any case).
3. When looking at individual arteries, the accuracy of the LAD was highest while that of the LCX was lowest. Contrary to LMS, LAD was shown to have the highest sensitivity. The sensitivity was highest for RCA and lowest for LAD.

RECOMMENDATION

1. To diagnose CAD and provide crucial information to guide treatment, therapy, and prognostic evaluation in patients with suspected CAD, CT coronary angiography is a first-line, noninvasive diagnostic test alternative to ICA.
2. In individuals with a moderate to low pre-test risk of CAD, for whom a diagnosis or exclusion of the condition cannot be made based on clinical examination alone, this test is invaluable.
3. In individuals experiencing chest pain other than from a heart attack, it can be used to quickly rule out coronary artery disease.
4. The impact of CT (128 and 256 slices) on diagnostic precision: a large cohort study.

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Original article

Two-Dimensional Speckle-Tracking Echocardiography to Monitor Left Ventricular Function After Percutaneous Coronary Intervention

A single center experience.

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Abstract:

- ***Background***: Conventional 2 D Doppler echocardiographic parameters are inadequate for evaluation and monitoring Left ventricle systolic function recovery of patients with ischemic heart disease (IHD) treated by Percutaneous coronary intervention (PCI). Hence, New strain imaging parameters are studied by using 2 D speckle Tracking Echocardiography. The aim is to compare the conventional echocardiographic parameters (Left ventricle ejection fraction, Wall motion score index, regional wall motion score) with speckle tracking echocardiographic parameters (Global longitudinal strain, Regional longitudinal strain) in patients with ischemic heart disease undergo Percutaneous Coronary Intervention (PCI).
- ***Method and patient:*** A prospective Interventional Hospital Based study enrolled 50 patients who had ischemic heart disease (IHD), Percutaneous coronary intervention (PCI) was done for them at IbN Al-Bittar Cardiac Surgery Center from October 2014 to April 2015. Both conventional echocardiographic parameters (Left ventricle ejection fraction, Wall motion score index, regional wall motion score according to coronary artery territory) and Speckle tracking echocardiographic parameters (Global longitudinal strain, Regional longitudinal strain according to coronary artery territory) done for them pre PCI, one day post PCI, and one month post PCI.
- ***Result:*** Regarding conventional echocardiographic parameters: Global LVEF pre PCI 52.34±90% , one month post PCI was (54.00±6.9), there was no significant difference statistically (P value 0.79), also Wall motion score index ,Regional wall motion score according to coronary artery territory were (1.22±0.25,1.44±1.52) respectively, one month post PCI were (1.98±0.26,1.40±0.58) respectively where there's no significant differences statistically (P value 0.25,0.22) respectively.

- Regarding speckle tracking parameters :Global Longitudinal strain for all patients pre PCI was (-14.30±3.54%) ,one day post PCI was (-14.78±3.81%) ;there was no significant differences (p value 0.77).After one month Global Longitudinal Strain was (-16.38±4.15%) where this consider highly significant differences (p value 0.001).Regional Longitudinal Strain according to the coronary artery territory pre PCI was (-14.49±4.47%),post one day post PCI was (-15.08±4.92%) where there's no significant differences (p value 0.10), while one month post PCI was (-17.70±5.27%),this was highly significant different statistically (0.001).Only in STEMI patients there was significant difference one day post PCI(P value 0.041 for Global LS,0.016 for Regional LS).
- ***Conclusions:*** In all IHD groups (STEMI, NSTEMI⁄UA, chronic stable angina) Speckle Tracking Echocardiographic parameters (Global Longitudinal Strain and Regional longitudinal strain) more reliable and effective than conventional echocardiographic parameters (Global LWEF,WMSI, RWMS) for monitoring improvement in LV systolic function post Percutaneous coronary intervention.

Keywords: Echocardiography, Two-Dimensional Speckle-Tracking Echocardiography, LV function.

INTRODUCTION

Non-invasive imaging detection of myocardial functional recovery is critically important in patients who undergo coronary heart disease (CHD) treatments such as CABG, PCI, and drug therapy. MRI is considered a standard strategy for this purpose. It can analyze myocardial deformation; mechanical characteristic accurately; However, MRI has its limitation for use in multiple point follow ups; high cost and time-consuming nature [(1)].

Echocardiography is a widely used noninvasive imaging modality for evaluating regional wall motion abnormality and left ventricular ejection fraction (LVEF) in patients with CHD.

Ejection fraction (EF) assessment has been consolidated as an accessible and reliable parameter in the quantification of the ventricular systolic function and it has also shown a huge value in welfare decisions and as prognostic indicator. However, exceptions to linearity between functional class and ejection fraction are large and they are placed at both sides of their value spectrum [(4)].

A new noninvasive ultrasound imaging technique that allows for an objective and quantitative evaluation of global and regional myocardial function independently from the angle of insonation and from translational movements [12-16]. STE is based on analysis of the spatial dislocation (referred to as tracking) of speckles (defined as spots generated by the interaction between ultrasound beam and myocardial fibers on routine 2-Dimensional sonograms). Before introduction of this sophisticated echocardiographic technique, only tagged magnetic resonance imaging (MRI) had enabled a myocardial dynamics [14].

The term speckle tracking implies that this technique is principally based on the analysis of speckles during the cardiac cycle. Single speckles are merged in functional units(kernels) that are in turn univocally identifiable given the peculiar disposition of the speckles. Speckle tracking echocardiographic –derived measurements has recently been validated sonomicrometry and tagged MRI, showing high feasibility and reproducibility [21]. Substantial potential limitations of this new technique are its strict dependence on the frame rate and high-quality 2-dimensional images. which are necessary for an optimal dentition of the endocardial border of apex and lateral wall [20].

The Aim of current study of this study is to compare the conventional echocardiographic parameters (Left ventricle ejection fraction by M mode, Wall motion score index, regional wall motion score) with speckle tracking echocardiographic parameters (Global longitudinal strain, Regional longitudinal strain) in patients with ischemic heart disease undergoing Percutaneous Coronary Intervention (PCI) for evaluation and monitoring of left ventricular systolic function.

PATIENT and METHOD

A prospective interventional hospital-based study was conducted at Ibn-AL Bittar Cardiac Surgery Center from October 2014 till April 2015.

Inclusion criteria: (1) patients with Recent ST-elevation myocardial infarction (STEMI) were admitted for diagnostic coronary angiography and possible Percutaneous coronary intervention (PCI) excluding cases of primary PCI.

(2) patients with Non STEMI or Unstable angina; admitted with indications for early diagnostic coronary angiography and possible PCI. (3) patients with chronic stable angina with indication for coronary angiography and possible PCI and had elective appointment for coronary angiography and possible PCI.

Exclusion criteria:(1) any patient with above diagnosis and not in sinus rhythm (2) patients with severe valvular heart disease (3) past history of PCI or CABG(4) Results of coronary

angiography revealed normal coronaries; non-significant coronary artery disease and three vessel disease referred for CABG (5) patients with poor acoustic window.

Baseline (1) conventional Two Dimensional Echocardiography (2DDE) parameters (Global left ventricle Ejection fraction by M mode where ≥ 55% consider the lower limit of normal, Wall motion score index and Regional wall motion score according to artery territory (2) Speckle tracking Echocardiography parameters(Global Longitudinal Strain and Regional Longitudinal Strain) taken within 24 hours prior to the diagnostic coronary angiography and possible PCI.

Regarding regional wall motion analysis by Two dimensional Doppler Echocardiography was based on the use of the 17-myocardial segment model that has been recommended by the American Society of Echocardiography and American Heart Association.

RESULTS

The total number of patients enrolled in the study was (56) . Six patients lost from follow up, so 50 patients were complete the follow up post one day and post one month, mean±SD age 54.20±9.47 years ,males were 40(80%),females were 10(20%),Hypertension was present in 23(46%),Diabetes Mellitus in 16(32%),Current smoking in 10(20%), Ex smoking in 17(34%). 20(40%) patients had STEMI, NSTEMI/unstable angina 20(40%),10(20%) had chronic stable angina. All undergoing PCI for appropriate indications. PCI done for LAD in 34(88%), RCA in 10(20%)and LCX only in (6) patients(12%) .This is showing in a Table (1).

Table 1. Baseline patient characteristics

Parameters	Total number (%)
Male **Female**	40(80%) 10 (20%)
Age ±SD(Years)	54.20±9.470
Hypertension	23 (46%)
Diabetes mellitus	16(32%)
Smoking Current smoking Ex smoking	27 (54%) 10 (20%) 17 (34%)

Coronary artery involved LAD LCX RCA	 34 (68%) 6 (12%) 10 (20%)
Groups STEMI NSTEMI/unstable angina Chronic stable angina	 20(40%) 20(40%) 10(20%)

**LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; STEMI:ST elevation myocardial infarction; NSTEMI: Non-ST Elevation myocardial infarction.*

Global LVEF pre PCI was (52.34±6.90%),one day post PCI was (52.34±6.90%), one month post PCI Global LVEF was (54.00±6.42%) where there's no significant differences (P-value 0.790). Wall motion score index (WMSI) ,Regional wall motion score (RWMS) for coronary artery territory of the target artery as determined by cardiologist pre PCI was(1.220± 0.25),(1.44± 0.527) respectively, one day post PCI was (1.220± 0.25),(1.44± 0.527) ; and one month post PCI was(1.19 ± 0.26, 1.40 ± 0.58) respectively, where there's no significant differences (P value 0.258, 0.226 respectively).This is showing in table (2).

Table 2. Comparison between conventional 2D echocardiographic parameters before PCI, and after PCI

Parameters	Size of sample	Pre PCI (mean ± SD)	One month post PCI (mean ± SD)	P.value
Global LVEF	50	52.34±6.90%	54.00±6.42%	0.79
WMSI	50	1.22 ± 0.25	1.19 ± 0.26	0.25
RWMS (Target vessel)	50	1.44 ± 0.52	1.40 ± 0.58	0.22

** The P.value> 0.05 is not significant. PCI: Percutaneous coronary intervention, Global LVEF: Global left ventricular ejection fraction, WMSI: Wall motion score index, RWMS: regional wall motion score*

Regarding Speckle tracking imaging, The Global Longitudinal strain(GLS) for all patients pre PCI was (-14.30 ± 3.54%) ,one day was(-14.78± 3.81%) , there was no significant differences(0.776) .After one month Global LS was (-16.38 ± 4.15%) where there's highly significant differences (0.001). Regional Longitudinal strain according to coronary artery territory of the target artery determined by cardiologist for all patients: mean Longitudinal

Strain was pre PCI (-14.49 ± 4.47%); one day post PCI was (-15.08 ± 4.92%),where there's no significant differences(p value 0.101) ,one month post PCI Regional LS was(-17.70 ± 5.27%),this was highly significant statistically(0.001). This is shown in Table (3) and figure (I).

Table 3. Comparison of 2 D Speckle tracking Echocardiographic parameters before PCI and after PCI

2 D speckle tracking echocardiograhic parameters							
Parameters	Sample size	Pre PCI (mean ± SD)	One day post PCI (mean ± SD)	P.value	Pre PCI (mean ± SD)	one month post PCI (mean ± SD)	P.value
Global Longitudinal Strain	**50**	**-14.30 ± 3.54%**	**-14.78 ± 3.81%**	**0.776**	**-14.30 ± 3.54%**	**-16.38 ± 4.15%**	**0.001**
Regional Longitudinal Strain of Target vessel	**50**	**-14.49 ± 4.47%**	**-15.08 ± 4.92%**	**0.887**	**-14.49 ± 4.47%**	**-17.70 ± 5.27%**	**0.001**

** The P.value> 0.05 is not significant, The P.value< 0.001 is highly significant PCI: Percutaneous coronary intervention.*

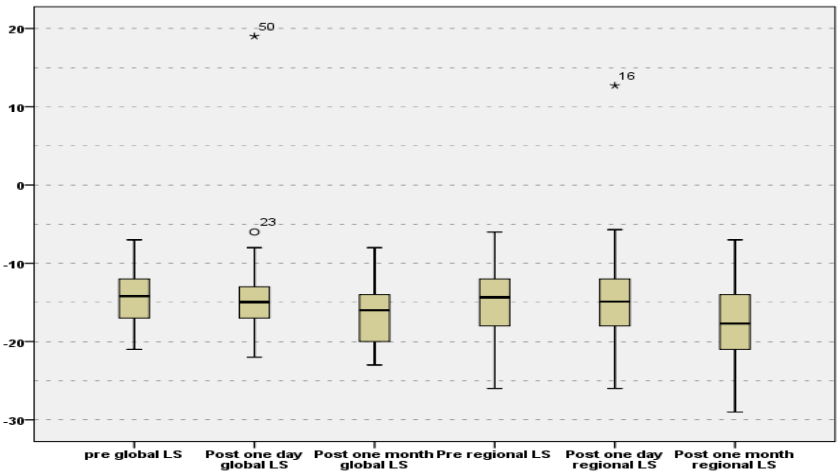


Figure I. Box plot graph comparison between global Longitudinal strain and regional Longitudinal strain pre Percutaneous intervention (PCI), one day PCI and one month post PCI.

Regarding specific groups: In STEMI patients; Global LVEF pre PCI was (49.70±6.18%),one day post PCI was (49.70±6.18%) , one month post PCI was (51.30±6.96%) There no significant difference statistically (0.700).Wall motion index score(WMSI), Regional wall motion score(RWMS) according to coronary artery territory of target artery determined by cardiologist was (1.36 ± 0.29 ; 1.71 ± 0.54) respectively, one day post PCI (1.36 ± 0.29 ; 1.71 ± 0.54), and post one month was(1.34 ± 0.34, 1.68 ± 0.57),also statistically no significant differences (p value 0.416, 0.198 respectively). This is shown in table (4).

Table 4. Comparison between conventional echocardiographic parameters before PCI and after PCI in STEMI patients.

Parameters	Size of sample	Pre PCI (mean ± SD)	one month post PCI (mean ± SD)	P.value
Global LVEF	20	49.70±6.18%	51.30±6.96%	0.70
WMSI	20	1.36 ± 0.29	1.34 ± 0.34	0.41
RWMS (Target vessel)	20	1.71 ± 0.54	1.68 ± 0.57	0.19

** The P.value> 0.05 is not significant, PCI: Percutaneous coronary intervention, LVEF: left ventricle ejection fraction, WMSI: wall motion index score, RWMS: regional wall motion score according to coronary artery territory.*

Regarding speckle tracking echocardiography; In STEMI patients pre PCI Global LS was (-12.45 ± 3.17%), one day post PCI was(-13.59 ± 3.58%) and it was significantly different (p value 0.041). After one month post PCI was (-14.58 ± 3.91%) ,this was significant difference (0.002). For Regional LS of coronary artery territory of target artery determined by cardiologist

pre PCI was (-12.68 ± 4.36%), one day post PCI was (-14.00 ± 4.96) ,this was significant difference (p value 0.016);After one month post PCI was (-15.59 ± 6.14%).and it was significantly different.(p value0.001) This showing in table(5);figure(II).

Table 5. Comparison between 2D Speckle tracking echocardiographic parameters before PCI and after PCI in STEMI patients.

2D Speckle tracking echocardiographic parameters							
Parameters	**Size of sample**	**Pre PCI (mean ± SD)**	**One day post PCI (mean ± SD)**	**P.value**	**Pre PCI (mean ± SD)**	**One Month post PCI (mean ± SD)**	**P.value**
Global Longitudinal Strain	**20**	**-12.45 ± 3.17%**	**-13.59 ± 3.58%**	**0.041**	**-12.45 ± 3.17%**	**-14.58 ± 3.91%**	**0.002**
Regional Longitudinal Strain (Target vessel)	**20**	**-12.68 ± 4.36%**	**-14.00 ± 4.96%**	**0.016**	**-12.68 ± 4.36%**	**-15.59 ± 6.14%**	**0.001**

** The P.value< 0.05 is significant. The P.value< 0.01 is highly significant; PCI: Percutaneous coronary intervention, STEMI: ST Elevation myocardial infarction*

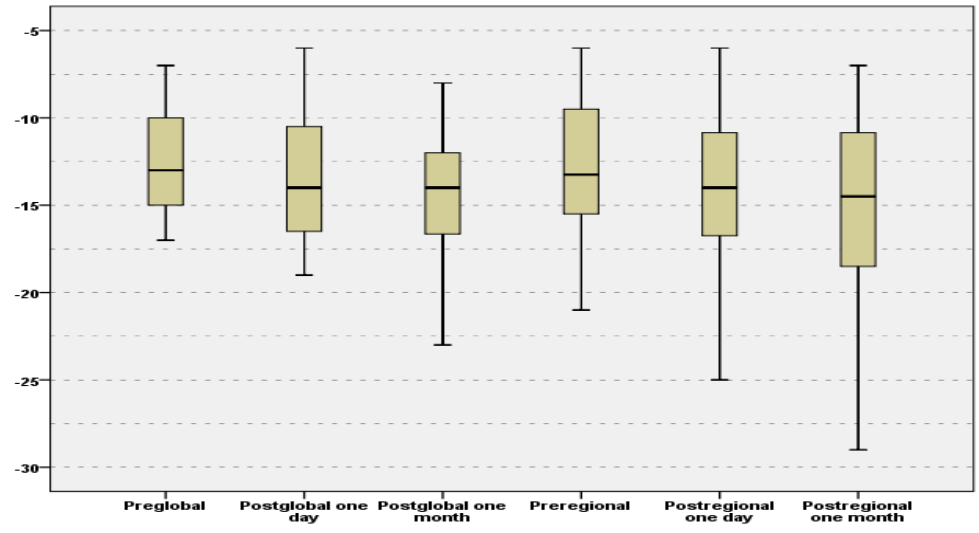


Figure II. Boxplot comparison between 2D Speckle tracking echocardiographic parameters before Percutaneous coronary intervention (PCI) and after PCI in ST Elevation Myocardial Infarction patients.

Regarding NSTEMI/Unstable angina patients: Pre PCI global LVEF (54.05± 6.84%), one day post PCI was(54.05± 6.84%) , one month was (55.70 ± 6.79%) where there's no significant differences(p value 0.361). WMSI; RWMS of coronary artery territory of target artery determined by cardiologist pre PCI was(1.15 ± 0.22; 1.33 ± 0.52) respectively .One day PCI was (1.15 ± 0.22; 1.33 ± 0.52) , one month post PCI was (1.13 ± 0.22, 1.29 ± 0.53) respectively ,it was not different significantly (p value 0.185,0.170 respectively).This is showing in table(6)

Table 6. comparison between 2D conventional echocardiographic parameters before PCI and after PCI in NSTEMI/UA patients

Parameters	Size of sample	Pre PCI (mean ± SD)	one month post PCI (mean ± SD)	P.value
Global LVEF*	20	54.05 ± 6.84%	55.70 ± 6.79%	0.361
WMSI*	20	1.15 ± 0.22	1.13± 0.22	0.185
RWMS (Target vessel)	20	1.33 ± 0.52	1.29 ± 0.53	0.170

** The P.value> 0.05 is not significant PCI: Percutaneous coronary intervention, NSTEMI: Non STEMI:UA: unstable angina, Global LVEF: Global left ventricular ejection fraction, WMSI: wall motion score index; RWMS: regional wall motion score.*

In NSTEMI/unstable angina patients the Global LS pre PCI was (-15.40 ± 3.66%),one day post PCI was (-15.33 ± 4.36%),it was not different significantly(0.82), and one month post PCI Global LS (-17.27 ± 4.25%) ,this was significantly different (p value 0.001),also for Regional LS of coronary artery territory of target vessel determined by cardiologist before PCI was(-15.59 ± 4.81%), one day post PCI was(-15.56 ± 5.35%) ,this was not different significantly (p value0.96).One month post PCI it was(-18.91 ± 4.74%) ,this was different significantly(0.001).This is showing in table (7);figure (III).

Table 7. Comparison between 2D Speckle tracking echocardiographic parameters before PCI and after PCI in NSTEMI/UA patients.

2D Speckle tracking echocardiographic parameters							
Parameters	Sample size	Pre PCI (mean ± SD)	one day post PCI (mean ±SD)	P.value	Pre PCI (mean ± SD)	One month post PCI (mean ± SD)	P.value
Global Longitudinal Strain	**20**	**-15.40 ± 3.66%**	**-15.33 ± 4.36%**	**0.820**	**-15.40 ± 3.66%**	**-17.27 ± 4.25%**	**0.001**
Regional Longitudinal Strain (Target vessel)	**20**	**-15.59 ± 4.816%**	**-15.56 ± 5.35%**	**0.969**	**-15.59 ± 4.816%**	**-18.91 ± 4.74%**	**0.001**

** The P.value> 0.05 is not significant. The P.value< 0.01 is highly significant; NSTEMI: Non- ST Elevation myocardial infarction, UA: unstable angina*

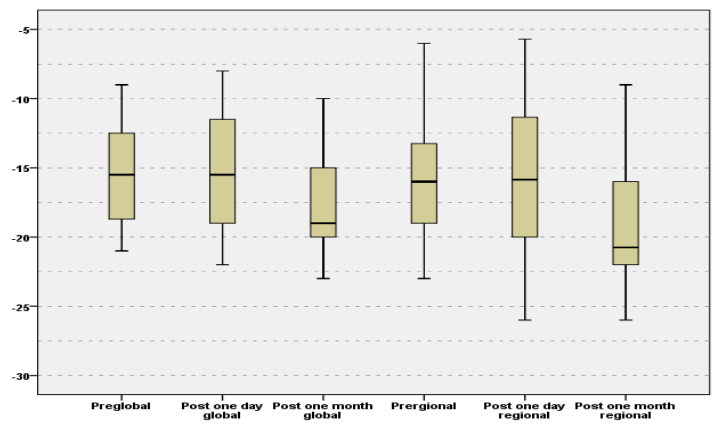


Figure III. Box plot comparison between 2D Speckle tracking echocardiographic parameters before Percutaneous intervention (PCI) and after PCI in Non -ST elevation myocardial infarction and unstable angina patients.

Regarding chronic stable angina patients pre PCI Global LVEF was (53.70± 5.22%) ,one day post PCI (53.70± 5.22%), one month PCI was (54.80±4.34%),there's no significant differences(p value 0.563).WMSI, RWMS according to coronary artery territory of target artery determined by cardiologist pre PCI (1.13 ± 0.188; 1.16 ± 0.20) one day post PCI and one month post PCI (1.13±0.188;1.16±0.20) there was no statistical difference .This showing in Table(8).

Table 8. comparison between conventional echocardiographic parameters before PCI* and after PCI in chronic stable angina.

Parameters	Size of sample	Pre PCI(mean ± SD)	1 month post PCI(mean ± SD)	P.value
Global LVEF*	10	53.70 ± 5.22%	54.80±4.34%	0.563
WMSI*	10	1.13 ± 0.18	1.13 ± 0.18	---
RWMS Target (vessel)	10	1.16 ± 0.20	1.16 ± 0.20	---

**The P. value> 0.05 is not significant The P. value is not calculated because of the mean ± SD are equal (The difference is zero) .PCI: Percutaneous coronary intervention, Global LVEF: Global left ventricle ejection fraction, WMSI: Wall motion score index, RWMS: Regional wall motion score.*

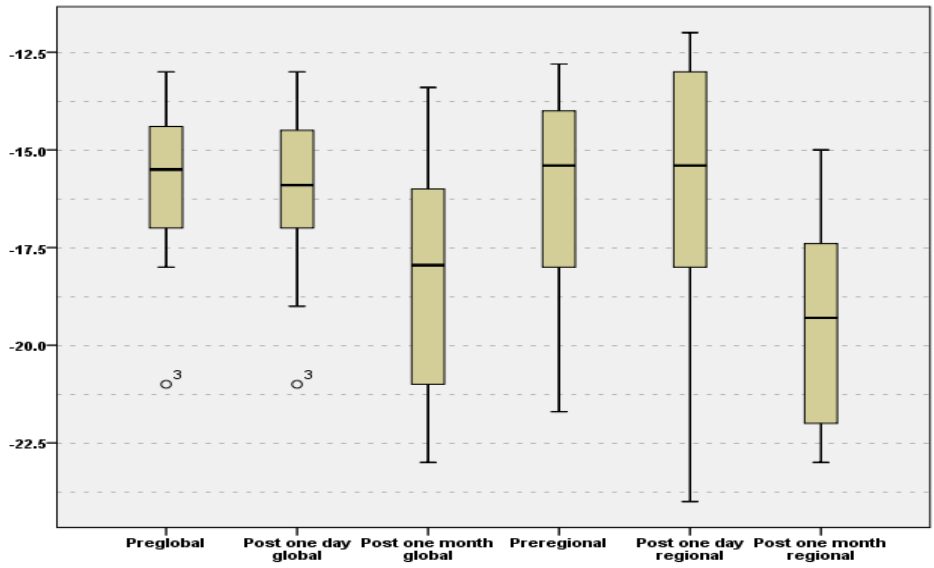
In chronic stable angina patients Pre PCI Global LS was (-15.83 ± 2.38%), one day post PCI was (-16.07 ± 2.44%) ,it was not significant (p value0.089),one month post PCI was (-18.28 ± 3.29%),it was significantly different(p value 0.042). For Regional LS according to coronary artery territory of target artery determined by cardiologist pre PCI (-15.91 ± 2.78%), one day post PCI (-16.26 ± 3.83%) was not significant statistically. After one month post PCI was (-19.50 ± 2.71%) this was significant statistically(p value 0.018) as shown in table (9);figure(IV).

Table 9. Comparison between 2D Speckle tracking echocardiographic parameters before Percutaneous coronary intervention (PCI) and after PCI in chronic stable angina

2D Speckle tracking echocardiographic parameters							
Parameters	**Sample size**	**Pre PCI (mean ± SD)**	**one day post PCI (mean ± SD)**	**P.value**	**Pre PCI (mean ± SD)**	**One month post PCI (mean ± SD)**	**P.value**
Global Longitudinal Strain	**10**	**-15.83 ± 2.38%**	**-16.07 ± 2.44%**	**0.089**	**-15.83 ± 2.38%**	**-18.28 ± 3.29%**	**0.042**
Regional Longitudinal Strain (Target vessel)	**10**	**-15.91 ± 2.78%**	**-16.26 ± 3.83%**	**0.609**	**-15.91 ± 2.78%**	**-19.50 ± 2.71%**	**0.018**

** The P.value> 0.05 is not significant., PCI: Percutaneous coronary intervention*

Strain values (%)



duration of follow up

Figure IV. Box plot comparison between 2D speckle tracking echocardiographic parameters before Percutaneous coronary intervention (PCI) and after PCI in chronic stable angina patients.

DISCUSSION

The current study revealed that the conventional echocardiographic parameters (Global LVEF, WMSI, RWMS according to coronary artery territory of target vessel as determined by cardiologist) measured by conventional echocardiography did not change significantly after successful PCI of the target vessel in all three studied groups of patients (STEMI, NSTEMI / Unstable angina, chronic stable angina).This finding may be due to the fact that these parameters are not direct measurement of improvement of myocardial function and depends on many other biological factors such as preload; afterload ;valve function, heart rate and others [48].

Our findings indicate that the speckle tracking parameters (Global Longitudinal Strain; Regional Longitudinal Strain according to coronary artery territory of target vessel as determined by cardiologist) were more effective and better reflected post PCI left ventricle myocardial function recovery than conventional echocardiographic parameters , this is in agreement with Caracciolo et al [24] study which indicate that Longitudinal strain mechanics were the primary predictors of improvement in global LV function rather than radial mechanics and LV wall thickening as determined by WMSI in patients with acute myocardial infarction treated by PCI. Also current study agreed with S. Cimino et al [49] study which indicate that

Longitudinal Strain (GLS) and Regional Longitudinal Strain (RLS) evaluation provides an accurate assessment of global LV myocardial function in patients with acute coronary syndrome where the cardiac MRI was the gold standard in that study, and the study only took into account the Longitudinal strain, where circumferential and radial strain considered not so reliable.

Our finding also agreed with Erdogan et al [50] study which revealed that in patients with chronic stable angina with chronic total occlusion followed before PCI and one month after PCI. In this study they use 3D echocardiography as the gold standard, and they found that the improvement in both left ventricle function based on 2D speckle tracking echocardiography parameters (Global Longitudinal Strain) and 3D Echocardiographic parameters (LVEF) are both correlated ,and are consistent with contrast enhanced MRI in other studies [51].

Our study showed that by speckle tracking echocardiography the significant improvement in LV systolic function in both STEMI and UA/NSTEMI patients was more significant than in patients with chronic stable angina and this may be explained that many patients of recent STEMI and UA/NSTEMI had acutely stunning myocardium, most of them had single vessel disease and the Target vessel for which PCI had been done is mostly the culprit lesion ; while in patients with chronic stable angina may had chronic stunning myocardium , have more than one vessel disease and the Target vessel where PCI had been done not necessarily the culprit lesion.

Recently Global Longitudinal Strain (GLS) included in the American society of echocardiography (ASE) Guidelines 2015 as an important prognostic parameter for evaluation of LV systolic function [44].

If our thinking for assessment of left ventricle systolic function is limited to the Ejection Fraction parameters, we may lose the options of an early diagnosis LV systolic dysfunction and recovery after revascularization. So new speckle tracking parameters facilitate a more comprehensive understanding of the pathophysiology that will allow us more efficient therapeutics.

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Conflicts of interest:

There are no conflicts of interest**.**

CONCLUSION

1.LVEF is a different component to deformation parameters and two Dimensional or M-mode is not the true volume measure. Auto EF is now available and may be more reliable.

2.Speckle Tracking Echocardiography being rather objective tool to decrease eye ball effect.

3.Strain imaging is a real myocardial functional parameter and mechanics reflecting the global myocardial function and performance.

4.Two Dimensional speckle tracking echocardiographic parameters (GLS,RLS) superior to conventional two Dimensional echocardiographic parameters (LVEF,WMSI,RWMS) for monitoring of both global and regional LV systolic function recovery post PCI.

RECOMMENDATIONS

(1) Our finding can be applicable in a daily practice as every patient which planned for PCI; conventional echocardiographic parameters especially Global LVEF should be combined with Global LS before the procedure or immediately after the procedure; so that the patient can be followed in the future for the recovery of myocardial function or for the development of new ischemia or complications after PCI as an objective rather than subjective judgment.

(2) In the future more studies can be done for:

1.Judgment of the extent of myocardial jeopardy.

2.Localization of coronary territory of coronary artery lesion.

3.determination of myocardial viability in cases of acute sever Left ventricle dysfunction or chronic ischemic cardiomyopathy before attempting PCI.

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Original article

Generalized Anxiety Disorder among Adult patients attending psychiatric clinic at Baghdad Teaching Hospital

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Abstract:

- ***Background***: Generalized anxiety disorder is characterized by chronic and persistent worry, which is multifocal, excessive, and difficult to control, and accompanied by nonspecific psychological and physical symptoms. The objective of the study is to determine the proportion of GAD, evaluate clinical symptoms with socio-demographic data and determine whether such patients have co-morbid mental illnesses.
- ***Method and patient:*** This cross sectional study was conducted at Baghdad teaching hospital, 263 patients included, the study took 17 weeks starting in June 2021 till mid-October 2021.
- ***Result:*** 2.6% of patients (7 patients from 263) found to have GAD, men and women were almost equally affected, most of the patients were employed and married, had secondary school achievements and all of them were from urban areas. Restlessness and irritability were the most frequent symptoms and sleep disturbance was the least among other symptoms. Depression was the most frequent comorbid illness; other anxiety disorders and personality disorder were the least comorbidities.
- ***Conclusions:*** The proportion of GAD is slightly lesser than other studies, higher proportion seen in older adults than the younger patients, common symptoms of GAD are also seen in other psychiatric disorders leading to under-diagnosing of the illness, and mental health comorbidities are high among patients with GAD, mainly depression.
- **Keywords:** Generalized anxiety disorder, baghdad teaching hospital, restlessness, irritability.

INTRODUCTION

Generalized anxiety disorder (GAD) is characterised via the means of continual worry. This worry, that's multifocal (e.g., approximately finances, family, health, and the future), excessive, and hard to control, is normally observed through different nonspecific mental and bodily signs and identified in line with DSM V criteria (appendix B). The term GAD can also additionally incorrectly means that the signs are nonspecific and this misunderstanding can cause inappropriate use of this terminology for nonspecifically any anxious patient [(1)].

Depending on the representative epidemiologic studies, the estimated prevalence of GAD in the general population of the United States was 3.1 percent last year and 5.7 percent over a patient's lifetime; the prevalence is roughly twice as high in women as it is in males[(2)]. The onset age of generalized anxiety disorder varies greatly; some instances begin in childhood, the majority in early adulthood, and another peak of new-onset cases occurs in older adulthood, frequently in the setting of chronic physical health issues [(3)]. Generalized anxiety disorder is particularly common in primary care centers, where 7 to 8% of patients suffer from it [(4)]. Patients rarely report the worry as a symptom. The main presentation in primary health centers is bodily signs and symptoms which include gastrointestinal symptoms (for example abdominal pain) and headache [(5)]. In children GAD frequently represented as recurrent abdominal ache and different somatic complaints which can lead them to leave the school [(6)].

One of the commonest comorbid conditions is depression; major depression sometimes is difficult to distinguish from GAD because many of the manifestations of the disorder (e.g., fatigue and insomnia) overlap with those of depression [(7)]. In many patients, GAD is an underlying waxing and waning state, with periodic episodes of major depressive disorder in particularly stressful life circumstances. This dual occurrence of GAD and major depressive disorder constitutes a condition sometimes referred to as anxious depression, which is a common clinical presentation in primary health centers[(8)].

Generalized anxiety disorder increases the risks of different mental and physical health conditions (e.g., chronic pain syndromes, asthma or chronic obstructive pulmonary disease, and inflammatory bowel disease [(9)].

35% of GAD patients self-medicate themselves with alcohol and drugs to reduce their symptomatology and this pattern of use contribute to the increased risk of alcohol- and drug-abuse among these patients [(10)]. Known risk factors of GAD include female sex, low socioeconomic status, and exposure to childhood adversity (e.g., physical or sexual abuse, neglect, and violence, alcoholism, and other drug use problems of the parents [(11)]. Physical

punishment in exposure in childhood is associated with an increased risk of GAD during adulthood [12].

Twin studies shown moderation in genetic risk of the disorder, while the heritability is between 15 and 20%.[13] Candidate and genome wide association studies suggested some genetic associations [13, 14], but these outcomes need to be widely replicated and studied. A psychological term known as intolerance of uncertainty — the habitude of an individual to become anxious when facing uncertain situations — shown to be a relatively specific characteristic of patients with GAD [15]. Although it is unclear whether the origin of this habitude is experiential or genetic, the observation of decreasing intolerance of uncertainty is an important factor for the outcomes of cognitive behavioral therapy provides support for its central role in this disorder [16].

Functional neuroimaging studies for individuals with GAD have suggested increased activation within parts of the limbic system (e.g., the amygdala) and reduced activation in the prefrontal cortex, and the functional connectivity between these regions [17-18].

Individuals with GAD generally have (Yes) response to the question Do you worry excessively about minor matters? This is needed to be asked of patients with disturbed sleep, a blue mood, long-term gastrointestinal and pain symptomatology, or other unexplained recurrent health issues. The Generalized Anxiety Disorder 7-Item (GAD-7) Questionnaire is a brief questionnaire that can be used to search and to follow up the disorder. ([19].

Some types of pharmacotherapy, psychotherapy, or both can be used for GAD patients [20-21]. A stepped-care approach is recommended. The first choices usually depend on the preference of the patients ([22]. Physicians not only the psychiatrists often can prescribe medications and follow the outcomes in such patients [23, 24].

Clinical experience and RCT provide evidence for exercise for anxiety, but the effect sizes are modest [25].

Pharmacotherapy reduces suffering and disability and results in improvement in health-related quality of life [26]. Efficacy of most (but not all) antidepressants had been supported by evidences, several benzodiazepines, pregabalin and buspar (buspiron) can be used in patients with GAD [27]. Selective serotonin-reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are generally considered to be first-line pharmacotherapies for GAD [20, 28]. There is no superiority in the efficacy of any medication in the classes of SSRI or SNRI in the treatment so the cost, the previous response to medication and the patient's preference makes the choice for the medication [29]. There is growing evidence for the use of

both aforementioned classes of medications for the treatment of anxiety disorders, including GAD, in children and adolescents [30]. Several RCT have shown a benefit of a newly marketed antidepressant, vilazodone [31]. Trials involving patients with GAD haven't shown effect for some other antidepressants, including bupropion and vortioxetin [32], so as a result these agents aren't recommended. The efficacy of imipramine which is an example of tricyclic antidepressants is similar to that of SSRIs.[28] In similar cases, alternative or additive therapies may be given; these include buspirone [33], pregabalin (not approved by the [FDA] for GAD), but has been shown to be efficacious [34], and quetiapine [35]. Limited data have suggested efficacy of antihistamines such as hydroxyzine for GAD, these are not recommended because of their sedative effect and absence of long-term evidence supporting the use of such medications [36]. Because the concerns about misuse and dependence, benzodiazepines for example valium are not administered for anxiety disorders including GAD By some clinicians [37].

Psychotherapeutic techniques for GAD, include cognitive behavioral therapy, psychodynamic therapies, mindfulness-based therapies [38], and applied relaxation therapy. Cognitive behavioral therapy involves cognitive restructuring, exposure, and relaxation training [39], cognitive behavioral therapy which can be delivered using Internet may be a perfect point to start with for some patients [40], especially those who cannot visit a therapist in person. The aim of this study is to ddetermine the proportion of GAD among patients attending psychiatry clinic at Baghdad Teaching hospital, evaluate the Socio-demographic data (gender, age, occupation, educational level, marital status and the residency) and clinical symptoms of GAD and determine whether patients with GAD have comorbid mental illnesses.

PATIENT and METHOD

The study was conducted at Psychiatric outpatient clinic in Baghdad Teaching hospital that is in the center of the capital, Baghdad city; the General hospital contains nearly most specialties and psychiatric clinic. It is one of the many public psychiatric outpatient clinics in Baghdad city which has relatively 7.1 million populations.

There are around 20 patients attending daily for various disorders and illnesses including those referred from other clinics,

This is a cross sectional observational study, 263 patients included in the study after taking their consent, the questionnaire was filled via person to person interview individually. The questionnaire contains 4 parts: the 1st one is the socio-demographic data, containing gender, age, occupation, marital status, education level, and living area. while 2nd part consisted of DSM5 diagnostic criteria of GAD and whether the patients met the criteria or not, 3rd part had

clinical symptoms related to GAD which was derived from DSM5 criteria; (restlessness, irritability, decreased concentration, easily being fatigued, sleep disturbance, and muscle tension), the final part had the common comorbidities that might associate GAD including depression, other anxiety disorders, substance use disorder, personality disorder, all are diagnosed based on DSM V criteria for the mentioned disorders.

The study took nearly 17 inconsecutive weeks for data collection, once weekly, each Wednesday, from 8:30 am. to 1 pm, spending almost 20 minutes with each patient the study started in early June 2021 till mid-October 2021.

Any adult individual aged 18-60 years who accepted to participate in the study were included whereas patients who were un-amenable, incommunicable, and those with severe cognitive and intellectual disabilities were excluded.

Ethical considerations involve the scientific and ethical committees of Iraq board of psychiatry thoroughly evaluated and accepted the researcher proposal. The participants got informed about the nature of the study, consent was taken verbally, and finally they were reassured regarding the secrecy and the confidentiality of their identity, and their information will only be used in for research purposes.

The collected data were introduced into Microsoft excel, and word using a personal laptop. Descriptive statistics including frequencies and percentages of the data were presented in tables and graphics.

RESULTS

Socio-demographic data

Total number of patients included in the study was 263 patients, 7 (2.66%) of them suffered from GAD, nearly half of all participants were men 147 (55.89%) and 116(44.1%) were women those who suffered from GAD were 4 men (1.52%) and 3 women (1.14%).

Almost less than 1/3 of all participants 75(28. 51%) aged between 30-39 years, 2(0.76%) of them had GAD, [3 (1.14%)] patients with GAD fell in the category of age 50-59 years, 1(0.38%) patient who suffered of GAD fell in the category 18-19 years and another was in the category 40-49 years

Occupation-wise, almost one quarter 71 (26.99%) of participants were either employed, 4 (1.5209%) of them met DSM5 criteria for GAD, or free lancers 69 (26.23%), 2 (0.76%) of them

had GAD. Almost half, 123 (46.768%), of the study contributors were unfortunately not working at the time of sample collection, amongst them only 1 (0.38%) had GAD.

Marriage amongst the participants had the biggest portion, 124 (47.14%) members were married, two of them (0.76%) had GAD, 39 (14.82%) were divorced; 3 (1.14%) of them suffered from GAD, while one quarter 69 (26.23%) of all members in the current study were single; 1 (0.38%) of them had GAD, finally the least portion was the widowed, 31(11.7870%) individuals ,of them 1 (0.3802%) had the disorder.

Regarding education level, almost one quarter of all participants were either illiterate or had finished primary school, while none of GAD patients in our study were uneducated, 1 (0.7604%) patient had finished primary school, more than tierce 103 (39.1634%) patients had completed secondary school, 3 (1.1406%) of them had GAD, finally 29 (11.0266%) of the participants were highly educated with a college degree in different specialties, 2 (28.5%) of them had met the criteria for GAD.

The subgroups of patients in the living area section were two, the major share living in the city 204 (77.5665%); 7(2.6615%) of them diagnosed with GAD, and 59 (22.4334%) were living in rural areas but none of them had GAD.

Table 1: Sample distribution according to gender

Variable	*n*./ (%)	Total number of GAD/ (%)	Percentage (%)
Gender Male	147 (55.893%)	4 (1.5209%)	57.1%
Female	116 (44.106%)	3 (1.1406%)	42.8%
Total	263 (100%)	7 (2.6%)	100%

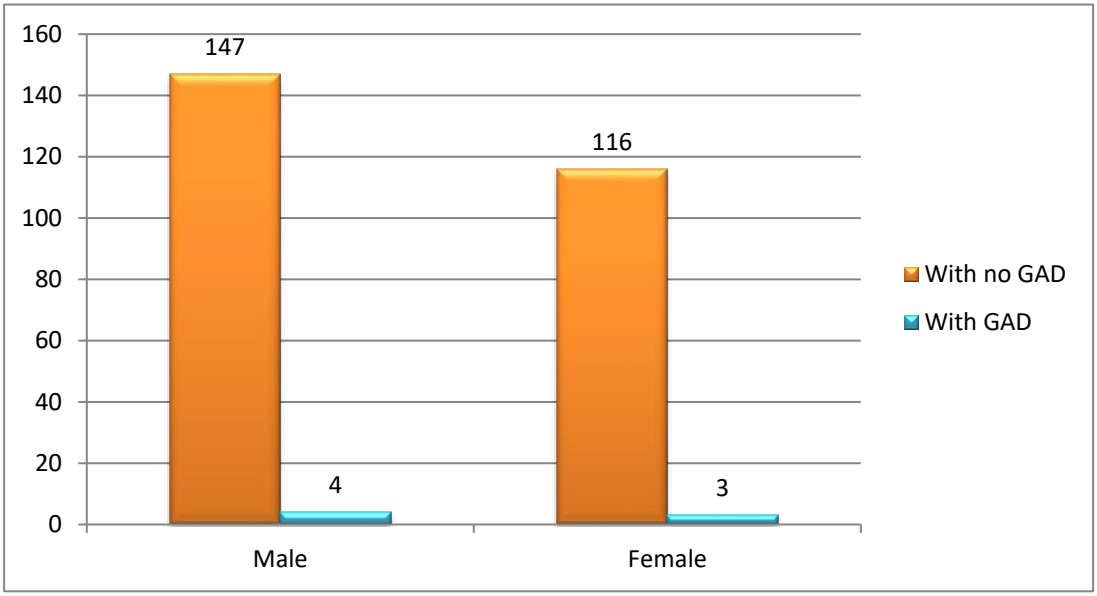

Figure 1: Sample distribution according to gender

Table 2: Sample distribution according to Age

Variable	*n.*/ (%)	Total number of GAD/ (%)	Percentage (%)
Age in years			
18-29	56 (21.29%)	1 (0.38%)	14.2%
30-39	75 (28.51%)	2 (0.76%)	28.5%
40-49	63 (23.95%)	1 (0.38%)	14.2%
50-60	69 (26.2%)	3 (1.14%)	42.8%
Total	263 (100%)	7 (2.6%)	100%

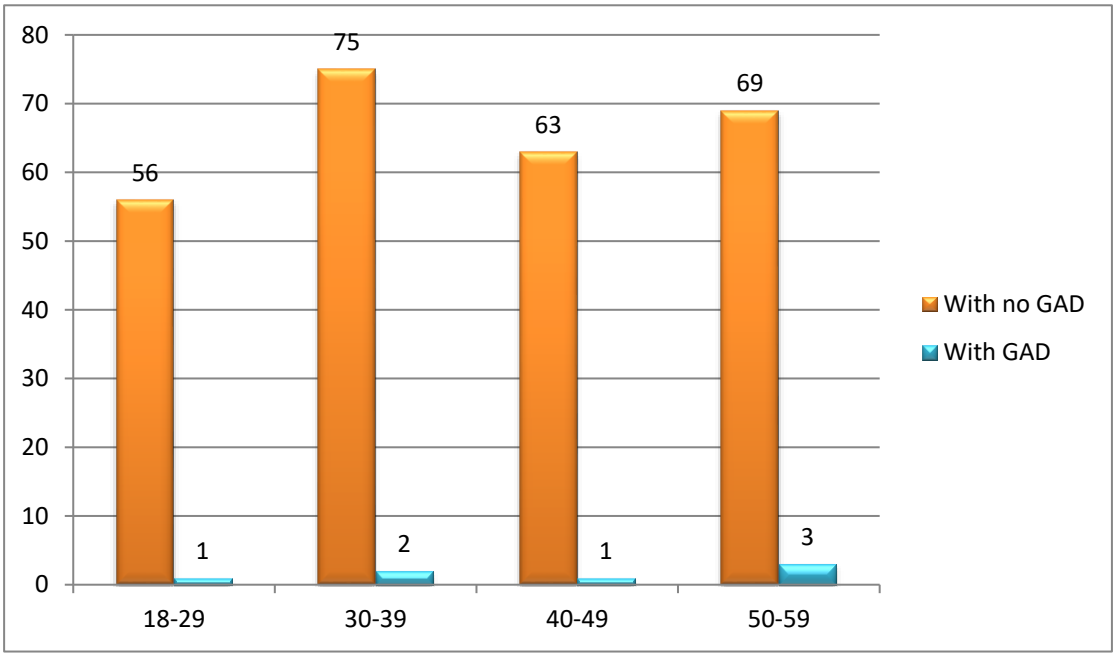

Figure 2: Sample distribution according to Age

Table 3: Sample distribution according to Occupation

Variable	*n.*/ (%)	Total number of GAD/ (%)	Percentage (%)
Occupation			
Employed	71 (26.99%)	4 (1.52%)	57.1%
Unemployed	123 (46.76%)	1 (0.38%)	14.2%
Free lancer	69 (26.23%)	2 (0.76%)	28.5%
Total	263 (100%)	7 (2.6%)	100%

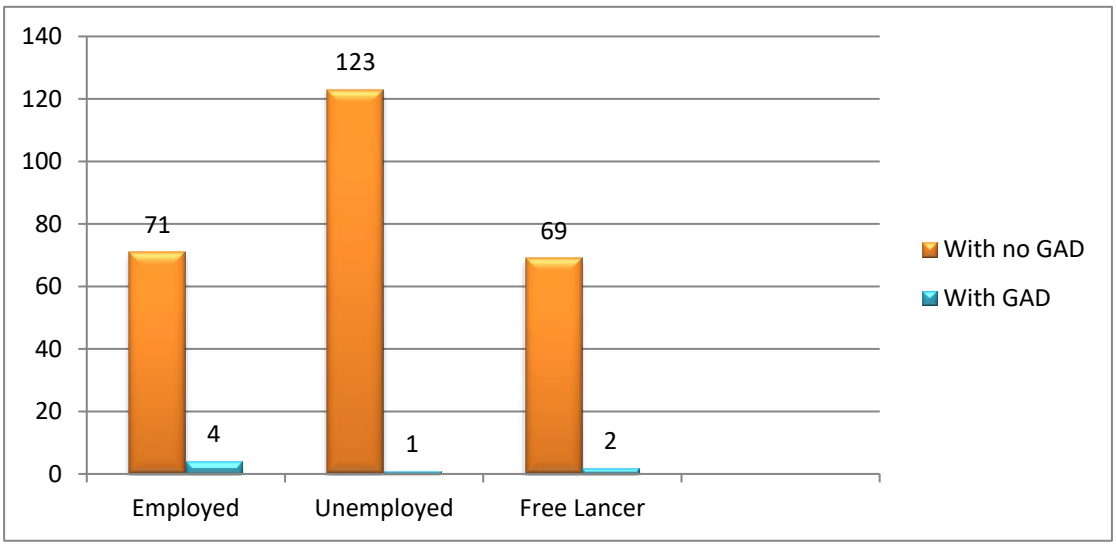

Figure 3: Sample distribution according to Occupation

Table 4: Sample distribution according to Marital Status

Variable	*n.*/ (%)	Total number of GAD/ (%)	Percentage (%)
Marital status			
Single Married	69 (26.23%)	1 (0.38%)	14.2%
Divorced	124 (47.14%)	2 (0.76%)	28.5%
Widowed	39 (14.82%)	3 (1.14%)	42.8%
	31 (11.78%)	1 (0.38%)	14.2%
Total	263 (100%)	7 (2.6%)	100%

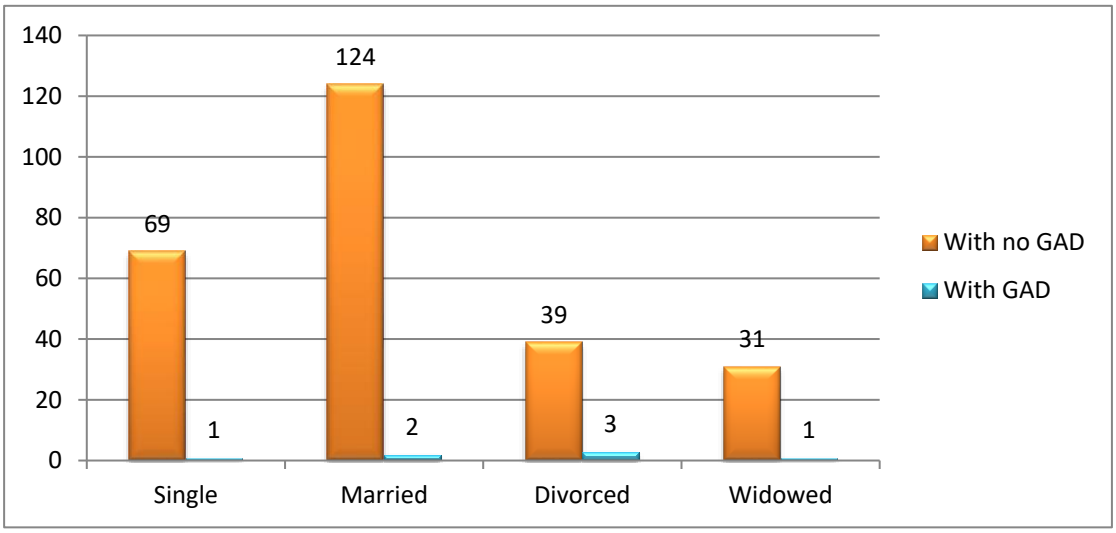

Figure 4: Sample distribution according to Marital Status

Table 5: Sample distribution according to Educational Level

Variable	*n.*/ (%)	Total number of GAD/ (%)	Percentage (%)
Education level Illiterate	67 (25.74%)	-----	-----
Primary	64 (24.33%)	2 (0.76%)	28.5%
Secondary	103 (39.16%)	3 (1.14%)	42.8%
University	29 (11.02%)	2 (0.76%)	28.5%
Total	263 (100%)	7 (2.6%)	100%

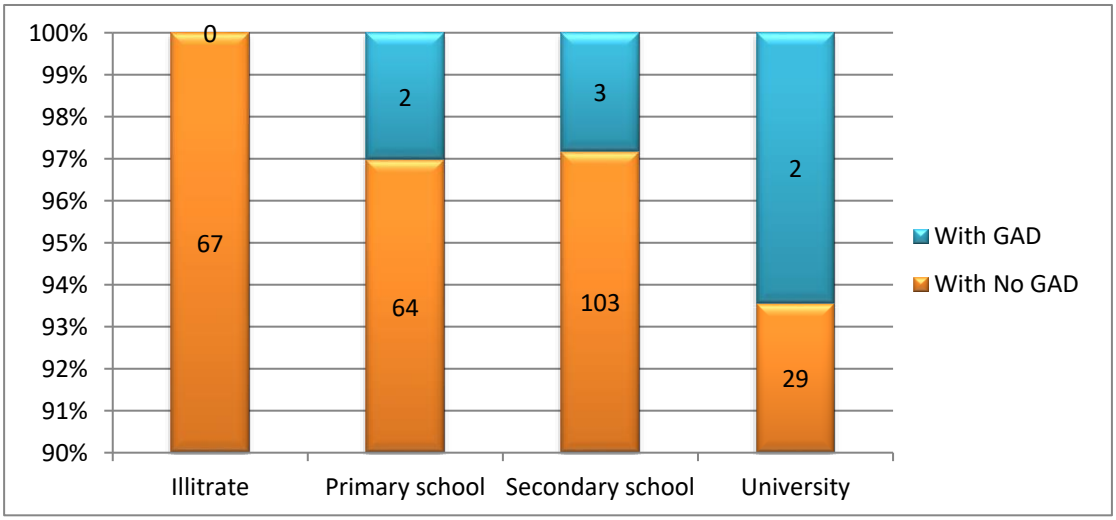

Figure 5: Sample distribution according to Educational Level

Table 6: Sample distribution according to Residency

Variable	*n.*/ (%)	Total number of GAD/ (%)	Percentage (%)
Living area Urban Rural Total	 204 (77.56%) 59 (22.43%) 263	 7 (2.6%) ----- -----	 100% ----- -----

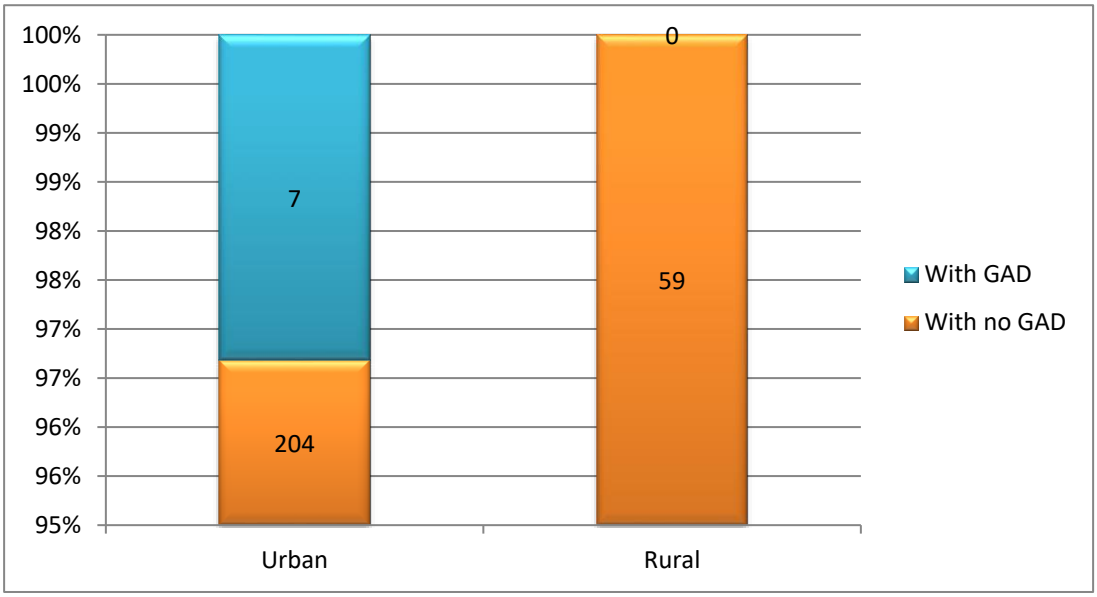

Figure 6: Sample distribution according to Residency

Clinical variables: In the current study all the participants had suffered from some symptoms seen in GAD, 157 (57.1749%) of the participants had restlessness but only 7 (2.6%) met the diagnostic criteria for GAD, 143 (54.3726%) of members in the study had fatigability, while just 5 (1.90%) of them diagnosed as having GAD, 149 (56.6539%) of participants suffered from difficulty concentrating or mind going blank, only 4 (1.52%) individuals met the criteria for GAD,129 (49.049%) of participants had symptoms of muscle tension and 4 (1.52%) met the criteria for GAD. Lastly sleep disturbance had the biggest share, 189 (71.8631%) among the participants, but only 2 (0.76%) did meet the criteria to diagnose GAD.

Table 7: clinical variables and characteristics of Generalized Anxiety disorder

Clinical symptoms	*n.* (%)	Frequency Among Patients with GAD	Percentage %
Restlessness or feeling keyed up or on edge	157 (57.17%)	7 (2.66%)	100%
Being easily fatigued	143 (54.37%)	5 (1.90%)	71.42%
Difficulty concentration or mind going blank	149 (56.65%)	4 (1.52%)	57.14%
Irritability	168 (63.87%)	7 (2.66%)	100%
Muscle tension	129 (49.04%)	4 (1.520%)	57.14%
Sleep Disturbance	189 (71.86%)	2 (0.76%)	28.57%
Total	263 (100%)	7 (2.6%)	100%

Other mental comorbidities: The vast majority of patients in the current study diagnosed with GAD had comorbid depression, six out of seven (85.71%), another two patients with GAD (28.57%) had comorbid substance use disorder (one of them had alcohol use disorder and the other one had polysubstance use disorder) and only one out of seven (14.28%) had either personality disorder (cluster A) or other anxiety disorder.

Table 8: mental comorbidities with GAD

Comorbidities	Patient with GAD and comorbid illness	Percentage
Mixed anxiety and Depression	6 of 7	85.71%
Other anxiety disorder	1 of 7	14.28%
Substance use disorder	2 of 7	28.57%
Personality disorder cluster	1 of 7	14.28%

DISCUSSION

The main aim of the study was to identify the percentage of patients with GAD who attend psychiatry clinic which has shown to be around 2.6% of all patients, in comparison to a study done in the USA in 2014 by M. Burstein etal.[41](3.03%), and what found in western countries such as Canada 8.7% [42], this difference may be due to smaller sample size, timing of sample collection which was during COVID 19 pandemic, differences in cultural aspects, stigma

associates psychiatric illnesses, predomination of physical symptoms in anxiety disorders, misinterpretation of psychological symptoms for physical ones, lower psychological awareness in our culture, faulty referral systems among primary health centres, hospitals and among the clinics, and many patients are chronic visitors for psychotic disorders.

The study has shown no significant differences in gender, (1.52%) for men and (1.14%) for women in comparison to a study done in Canada in 2016 by Rita A. Watterson et al.[42], which found that 3.2% of GAD patients were women and 2% were men, this showed almost double proportion of GAD among women than among men , which is the case in the literature too, this differences in the current study mostly due to almost equal number of male and female contributors to the study, partially may be due to the discrimination for the illness noted more for women than men in our society, partially may be due to the discrimination for the illness noted more for women than men in our society.

Patients with GAD showed highest proportion for age group 50-60 years old (42.8%) followed by young age group 30-39 years (28.5%) and this was relatively similar to a study done by Corey S. Mackenzie et al.[43] in 2011 , which found that the highest proportion was for adults age 55 years or more while another study done by KatjaBeesdo et al.[44] in 2015 in Germany, found that GAD was more common among individuals aged 34 years which is similar to what's seen in literature, differences in our study may partially be explained by that anxiety usually accompanied by many physical symptoms which are not specific so that individuals spend the early years of their illness attending medical, rheumatological, neurological, and other clinics, and not until several years they start to develop awareness to their illness and attend psychiatry clinic, or may be because of the faulty referral system as mentioned earlier, also the lower the educational level of the contributors the more they misinterpret psychological symptoms for physical ones.

Marital state of patients with GAD was highest for the divorced (42.8%), similar to what's found in Rita A. Watterson et al.[42], while a study done in Singapore bySherilyn Chang et al.[45] in 2019, showed higher proportion for married individuals (59%), this may be because of divorced status is stressful and may contribute to unresponsiveness to treatment.

While the educational level of most patient with GAD in Singapore was mainly university achievement (29.4%)[45], this study showed highest percentage among those who had secondary school education (42.8%), this is may be due to increased number of those who cannot finish secondary school in our country because of poorer support and faulty educational system, lower educational level in our country, and partially may be due to people with secondary school achievements represents the majority of the participants in the study.

Nearly more than half of patients with GAD in this study were employed (57.1%), which is relatively similar to a study done by Sherilyn Chang etal.[45]

All of those who met GAD criteria were living in urban areas and none have lived in rural areas, this is may be due to the location of the hospital is in the centre of the city, and the referral system between the primary care centres in the rural areas and the psychiatry clinic is not working at its finest, therefore; the visitors were from urban areas.

All the patients attending psychiatry clinic suffered from symptoms seen in GAD, but only 2.6% met the criteria of GAD, in the current study all patients with GAD had restlessness and irritability in comparison to what's found in M. Burstein et al.[41], 71% of patients had restlessness and irritability, this might be due to the unspecificity of those symptoms which could be found in most psychiatric illnesses and might be associated with other medical disorders, sleep disturbance was the least compliant in our study (28,57%) in contrast to the proportion seen in M. Burstein et al.[41], this is may be because most patients in the study were already on medication which partially improve sleep alongside other symptoms of GAD, and may be due to substance use that was presented in 2 out of the 7 patients who were diagnosed with GAD.

Comorbid mental disorders with GAD was high in the study, especially depression (85.7%) but other anxiety disorder was (14%), in comparison to Corey S. Mackenzie et al.[43] and KatjaBeesdo et al.[44] in which other anxiety disorder was as common as depression, another study Sherilyn Chang et al.[45], found 27% of patients with GAD also had comorbid depression, the difference might be explained as most of patients with other anxiety disorders complain of many physical symptoms, and in some patients physical symptoms become the main concern, which in turn result in attending clinics other than psychiatry, and the referral system is not working at its best leading to missing of some cases.

Comorbid substance use was in our study (28%) was similar to M. Burstein et al.[41] which was (23%), but higher when compared to Corey S. Mackenzie et al.[43] (6.5%), this is due to smaller sample size in the study, lower academic achievements, social support, lower health awareness in the community, and mismanagement of patients.

Personality disorder was found in 14% of patients with GAD, which was lesser than what's seen in literature and in Corey S. Mackenzie et al.[43] because of smaller sample size, the lesser number of visits to make the diagnosis of personality disorder, and the time limit of this study. The limitations of the study can be abbreviated by the following points:

1. Data collection was obtained in the time when COVID 19 was pandemic and as a result of the fear from acquiring the infection, lead to fewer number of patients in the study.

2. The room of the interview was not comfortable and not private.
3. The findings in this study cannot be generalized neither to all Baghdad city nor all the country because it was conducted in a single hospital.
4. Small sample size for such study.

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Nil.

Conflicts of interest:

There are no conflicts of interest**.**

CONCLUSION

1. This is the first study done to identify GAD proportion at psychiatry clinic in Baghdad Teaching Hospital.
2. The proportion of GAD is slightly lesser than other countries.
3. There are no significant differences in gender.
4. Higher proportion seen in older adults than the Youngers.
5. Symptoms seen in GAD are also seen in other psychiatric illnesses leading to misdiagnosing of the illness.
6. Mental comorbid disorders are high among patients with GAD, mainly mixed anxiety and depression.

RECOMMENDATIONS

The study highlighted a greater attention to the following concerns;

1. Increasing psychiatric awareness amongst population specifically for GAD.
2. Decrease the stigma about psychiatric illness.
3. Enhance the referral system between the clinics and among hospitals and primary health centres.
4. Doing researches and taking larger sample size on a broader time limit.
5. Including other psychiatric hospitals to have more precise representation for the city.
6. To do similar studies at primary health centres.
7. Doing a screening assessment for GAD using scales for most patients who attend the psychiatric clinics.

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Original article

Evaluation of Maternal Serum Homocysteine in Pre eclampsia

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Abstract:

- ***Background***: Pre-eclampsia affects about 2–8% of all pregnancies. It is one of the leading causes of maternal and perinatal morbidity and mortality hyperhomocysteinemia is considered as a risk factor for endothelial dysfunction and vascular disease. The vascular changes induced by homocysteine are similar to those with pre-eclampsia. The aim of the study is to identify the relationship between maternal serum homocysteine level and the development of pre-eclampsia.
- ***Method and patient:*** A case control study that was carried out in the Department of Obstetrics and Gynecology at Azadi Teaching Hospital in Kirkuk-Iraq, during the period of eight months from 1st of Feb. till 1st of October 2021. It included 80 pregnant women with singleton viable pregnancy, gestational age of > 20 weeks. They were divided into two groups: Case group included 40 pregnant women who had diagnosed as pre eclampsia (mild and severe) and control group included 40 healthy normotensive pregnant women. Patients with multiple pregnancy, history of medical disease or tacking treatment for hypertension were excluded from the study. Blood sample was taken from each woman for biochemical study, serum homocysteine level was measured using ELISA technique.
- ***Result:*** In this study, pregnant women with pre-eclampsia had significantly higher mean of serum homocysteine compared with controls. Homocysteine level > 8.95 µmol/l is a predictor for pre-eclampsia. Out of 40 women with pre-eclampsia, 42.5% were mild, while the remaining 57.5% were severe. Pregnant women with severe pre eclampsia had significantly higher mean of serum homocysteine compared to those with mild pre-eclampsia. The level of tested biomarkers and homocysteine was tested between the two study groups to assess their rule in pre eclampsia.
- ***Conclusions:*** Maternal serum homocysteine biomarker represents an early non-invasive marker for diagnosis of pre eclampsia and to name the disease according to the severity.
- **Keywords:** Hypertension, pre eclampsia, homocysteine, pregnancy.

INTRODUCTION

Pre eclampsia is an idiopathic disorder of pregnancy characterized by proteinuric hypertension, recent estimates indicates that over 30000 women die worldwide each year because of pre eclampsia and its complications, with 98% of these occurring in the developing countries. Globally, pre eclampsia has been estimated to cause between 10 and 25% of perinatal loss. Up to 5% of women will develop pre-eclampsia in their first pregnancy and although the overwhelming majority of these will have successful pregnancy outcomes, the condition can give rise to sever multisystem complications including cerebral haemorrhage, hepatic and renal dysfunction and respiratory compromise. The development of strategies to prevent and treat the disorders has been challenging due to an incomplete understanding of the underlying pathogenesis [(1).] New biomarkers could be significantly aiding the diagnosis of women suspected of having pre eclampsia. experts have long sought biomarkers for pre eclampsia that are reliable and can be measured with precision, and that can allow for an objective assessment of the disease, furthermore, because the presence of increased urinary protein is usually a late manifestation of the disease, it is hoped that the use of biomarkers would enable earlier detection or even prediction of the disease , some studies reported that high plasma homocysteine may be associated with adverse pregnancy outcomes, such as pre eclampsia [(2).]
Pre-eclampsia is defined as a new onset hypertension with significant proteinuria arising de novo after the 20th weeks of pregnancy in previously normotensive women and resolving completely by the sixth post-partum week [(3).] Significant hypertension defined as at least 140/90 mmHg recorded blood pressure on at least two separate occasions and at least four hours apart, significant proteinuria defined as a urinary protein/creatinine ratio greater than 30 mg/mmol or a validated 24-hour urine collection results showing greater than 300mg protein [(4,5)]
Pre eclampsia can originate in the placenta and may occur in the absence of fetal tissue (as in molar pregnancy) and its manifestations will only resolve following delivery of the placenta. The blueprint for establishing PE is determined at the outset of pregnancy when placental trophoblast invades the maternal uterine spiral arteries at the time of implantation .In pregnancies destined to be complicated by PE, transformation of the spiral arteries is impaired, with suboptimal remodeling of small-capacitance constricted vessels into dilated large-capacitance conduits , the prevailing theory has been that the subsequent relative placental ischemia causes release of vasoactive factors which then give rise to endothelial-mediated end-organ damage and clinical manifestations of PE [(1)].
Maternal characteristics and history provide strong clues to which women are at more risk of developing pre-eclampsia than others, particularly: Prior pre-eclampsia, chronic hypertension. ,multiple gestation ,pregestational diabetes mellitus, maternal BMI > 30 kg/m2 ,antiphospholipid syndrome/SLE ,and, assisted reproductive therapies [(6)].Other factors less

strongly associated with pre-eclampsia include, but are not limited to :advanced maternal age, family history of pre-eclampsia, short duration of sexual relationship(< 6 months) before the pregnancy, primigravida (although pre-eclampsia may occur in subsequent pregnancies even in the absence of pre-eclampsia in the first), Prim paternity , both changed paternity and an interpregnancy interval >5years have been associated with an increased risk for pre-eclampsia, chronic kidney disease, and, connective tissue disease [7].

Homocysteine is an amino acid not supplied by the diet, its levels vary between men and women with a normal range typically between 5-15 μmol/L. Hyperhomocysteinaemia is when levels more than 15 μmol/L. Hyperhomocysteinemia, or increased circulating levels of homocysteine, is generally recognized as an independent risk factor for coronary, cerebral, and peripheral atherosclerosis. The levels of homocysteine can be increased by defective metabolism of methionine, resulting from either mutation in genes coding for the enzymes of homocysteine metabolism, or deficiencies of certain vitamin cofactors. In addition to genetic alterations, vitamin deficiencies, and several other environmental factors as increased intake of methionine, certain medications are known to contribute to variations in homocysteine levels [8].

Hyperhomocysteinemia is considered as a risk factor for endothelial dysfunction and vascular disease just as is pre eclampsia . Over the past two decades, endothelial cell activation has become the center piece in the contemporary understanding of the pathogenesis of PE. The vascular changes induced by homocysteine are similar to those associated with PE and include atherosis and endothelial dysfunction resulting in blunted vaso-relaxation mechanism. Intact endothelium has anticoagulant properties, and it blunts the response of vascular smooth muscle to agonists by releasing nitric oxide [9].

Hyperhomocysteinemia appears to cause endothelial dysfunction through direct toxic and oxidative stress mechanism. The association of hyper-homocysteinemia and pre eclampsia has been suggested some authors in 1995 who demonstrated that homocysteine was seven times more common in women with history of severe pre eclampsia. Since then, there have been multiple studies concluding the strong association of hyper-homocysteinemia and PE [1].

PATIENT and METHOD

This study is a case control study that was carried out in the department of obstetrics and gynecology at Azadi Teaching Hospital in Kirkuk-Iraq, during the period of eight months from 1st of Feb. till 1st of oct. 2021. The study protocol was approved by the scientific council of obstetrics and gynecology / Iraqi Board for Medical Specializations, it included 80 pregnant women with singleton viable pregnancy, gestational age of > 20 weeks assessed by menstrual dates and proved by first trimester ultrasound scan visiting consultancy clinic or were admitted to the obstetric ward for assessment and management ,those women classified into two groups:

Case control; Included 40 pregnant women who had diagnosed as pre eclampsia (mild or severe).

Control control: Included 40 normotensive pregnant women without any known pregnancy complications and with matched gestational age.

women included in this study were singletone pregnancy, not in active labour, no signs of infection, received folic acid supplements until 12 weeks of gestation. women excluded from this study are those with gestational age < 20 week , essential hypertension suggested by history or documentation of hypertension in pregnancy state or hypertension before 20 weeks of gestation ,history of cardiovascular disease , history of pregestational and gestational diabetes mellitus, neurological disorders (like Alzheimer's coincidental seizure in pregnancy),renal impairment , premature rapture of membrane and chorioamnionitis, hematological disorders (like megaloblastic anemia),inflammatory or infective disorders drug history (methotrexate, PPI, nitric oxide, theophylline and phenytoin), history of smoking and alcohol intake.

RESULTS

The total number of study subjects included in the statistical analysis was 80, divided into two groups 40 pregnant women with pre eclampsia and 40 pregnant women with normal pregnancy.

The comparison between PE group and controls by certain demographic features showed that there were no statistically significant differences between the two groups in terms of age (P= 0.467) and BMI (P= 0.093) as shown in (Table 1)

Table 1. distribution of certain demographic characteristics between study groups

Characteristics	Study Groups		P – Value
	PE Mean ± SD	Control Mean ± SD	
Age (Years)	30.22 ± 6.02	31.3 ± 7.08	0.467
BMI (kg/m^2)	23.73 ± 3.4	23.09 ± 3.24	0.093

Regarding obstetrical characteristics, there were no statistically significant differences between the two groups in terms of parity (P= 0.787), and GA (P= 0.867) as shown in (Table 2)

Table 2. Distribution of mean obstetrical characteristic between study groups

Characteristics	Study Groups		P - Value
	PE Mean ± SD	Control Mean ± SD	
Parity	1.52 ± 1.76	1.42 ± 1.51	0.787
GA (Weeks)	36.92 ± 3.26	37.02 ± 1.88	0.867

there was a statistically significant difference in levels of SBP and DBP between the two groups. The means of SBP and DBP were significantly higher in PE group compared with control group (146.1 mmHg versus 119.8 mmHg, P= 0.001 and 103.3 mmHg versus 75.6 mmHg, P= 0.001, respectively) (Table 3)

Table 3. Comparison in mean levels of SBP and DBP between study groups

Biomarker	Study Groups		P - Value
	PE Mean ± SD	Control Mean ± SD	
SBP (mmHg)	146.1 ± 12.42	119.8 ± 10.22	0.001
DBP (mmHg)	103.3 ± 9.69	75.6 ± 10.63	0.001

In the present study, there was a statistically significant difference in homocysteine levels between the study groups. Pregnant women with PE had significantly higher mean of serum homocysteine compared with controls (154.8 ng/ml versus 66.33 ng/ml, P= 0.001) (Table 4 and figure 1)

Table 4. Comparison in mean level of homocysteine between study groups

Homocysteine (ng/ml)	Study groups		P - Value
	PE Mean ± SD	Control Mean ± SD	
	154.8 ± 79.46	66.33 ± 33.27	0.001

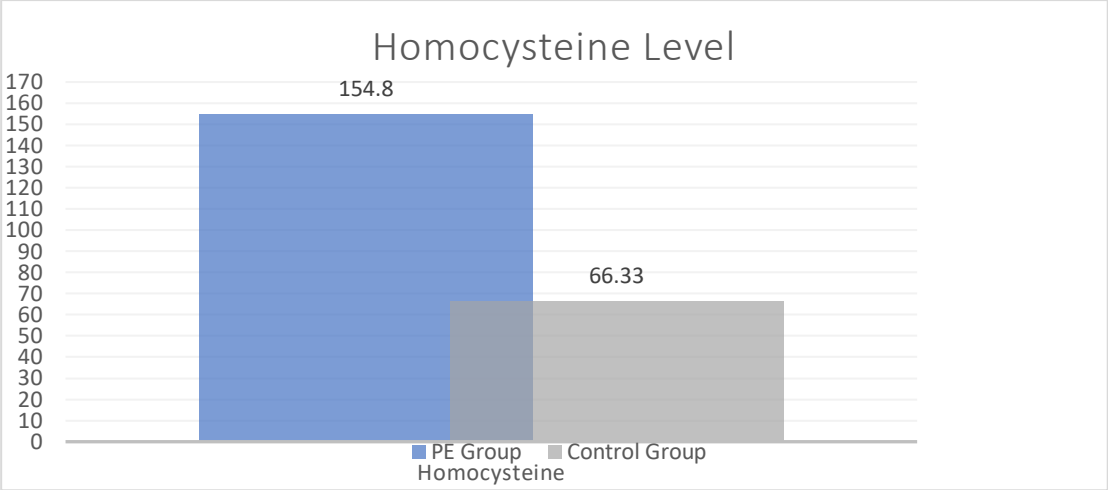

Figure 1. Distribution of study groups by mean level of homocysteine.

Receiver operating characteristic (ROC) curve analysis was constructed for homocysteine level as a predictor for PE. The cut point of the homocysteine level was 89.5 ng/ml. Hence, homocysteine level > 89.5 ng/ml is a predictor for PE, as a large significant area under the curve (AUC= 92.5%) indicating a significant association between the higher level of homocysteine and having PE. Homocysteine level was 90% sensitive, 87.5% specific, and 88.8% accurate in diagnosis of PE (Table5) and (Figure 2).

Table 5. Diagnostic accuracy of homocysteine level as a predictive marker for PE

Homocysteine Level (ng/ml)	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	89.5	**90%**	**87.5%**	**87.8%**	**89.7%**	**88.8%**

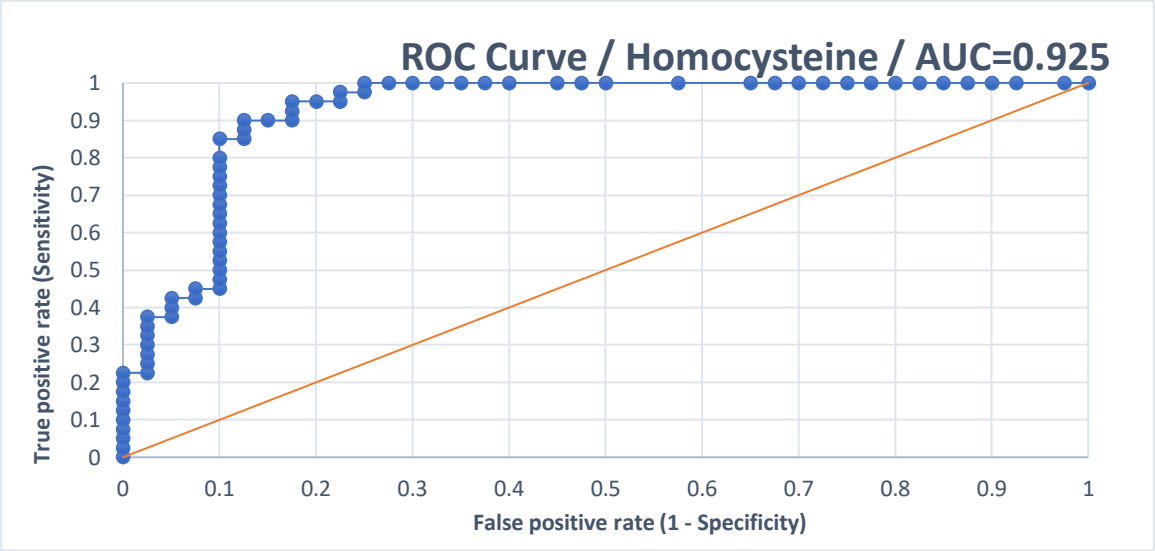

Figure 2. ROC curve for homocysteine in predicting of PE

It was clear that there was a statistically significant difference in homocysteine levels between patients of PE group. Pregnant women with severe PE had significantly higher mean of serum homocysteine compared to those with mild PE (192.3 ng/ml versus 102.8 ng/ml, P= 0.001) (Table 6).

Table 6. Comparison in mean level of homocysteine between PE group

Homocysteine (ng/ml)	PE Severity		P – Value
	Mild Mean ± SD	Severe Mean ± SD	
	102.8 ± 24.32	192.3 ± 85.1	0.001

DISCUSSION

Pre eclampsia (PE), a pregnancy specific syndrome, is a major cause of maternal and perinatal morbidity and mortality of all pregnancies. Despite a fairly high incidence,the underlying etiology of pre eclampsia is still incomplete[11] . Although the pathogenesis is still under investigation, impaired placental function seems to play a pivotal role in the etiology of this syndrome, it is hypothesized that pathophysiology of PE is characterized by a cascade of impaired early trophoblast invasion, decreased placental perfusion, placental ischemia,

oxidative stress, and consequentially impaired placental factors (imbalance in angiogenic and prothrombotic factors) which are playing a key role in inducing systemic maternal endothelial dysfunction[12]. Clinical evidence had reported a hyperhomocysteinaemia features in hypertensive disorders of pregnancy [13].

It is a risk factor for endothelial dysfunction and vascular disease like atherosclerosis. In normal pregnancy there is conversion of spiral arteries from its highly tortuous thick-walled vessels to flaccid sinusoidal conduits of low resistance, however, the muscular coats of spiral arteries are retained in pre eclampsia [14]. In PE there is elevated homocysteine injuries and abnormal vascular endothelium [9]. The main hypothesis of this study is that maternal homocysteine level may differ between pre eclampsia women and healthy pregnant women and also between sever and mild pre eclampsia patients.

The current study showed that the mean and standard deviation (SD) of age was 30.22 ± 6.02 years, and of of BMI of PE group was 23.73 ± 3.40 kg/m2, 60% of cases had normal weight; there were no significant differences between the two groups in terms of age (P= 0.467) and BMI (P= 0.093). An agreement reported by Al-Sakarneh and other co-authors in their study in 2021, in which no significant differences was observed between cases and controls in terms of age and BMI [14] another agreement was found in consistent with result of Dundar et al that found no statistical difference in BMI between studied groups[15], and in disagreement with the results observed in AlSheeha et, al. study in 2016, in which mean and standard deviation (SD) of age was 30.6±6.0 years, the mean and SD of BMI was 31.0 ± 6.3Kg/m2[16].

Concerning parity, 55% of cases were nulliparous. The GA was ≥ 37 weeks in 60% and 70% of the pregnant women in PE group and control group, respectively.

In this study, there were no significant differences between the two groups in terms of parity (P= 0.787), and GA (P= 0.867).This agrees with the findings of Ayala et al, 2001 in which no significant relation between parity and elevation of BP was observed, The larger, although not statistically significant, differences as a function of parity in our study were found for women ≥36 years of age; surprisingly, for both SBP and DBP measured at all 3 trimesters of pregnancy in this age group, multiparous women tend to have a slightly higher BP than do nulliparous women, in opposition to previous reports based on casual measurements ; a slightly higher BP can also be observed for all multiparous women compared with nulliparous women, independent of maternal age for data sampled by ABPM in the second trimester of pregnancy, although differences are not statistically significant[17].

However, it differs from the result of Košir Pogačnik, et al,2020 that showed multipara had a significant lower incidence of pre eclampsia[18].

Our study revealed a significant difference in levels of SBP and DBP. The means of SBP and DBP were significantly higher in PE group than control group (P= 0.001). The results in Al-Sakarneh,et al study in 2021, agreed to the current one, as SBP and DBP was significantly

higher in women with PE than in controls (154.16 ± 2.57 and 114.16±1.44 mmHg vs 95.16±1.05 and 75.33±0.89 mmHg, respectively, P < 0.001) [14] . In the same accordance, an agreement reported in a study conducted by Özdemir and colleagues in 2018, in which patients in the PE group, had a systolic and diastolic blood pressure significantly higher than that observed in patients of control group(P<0.001)[19].

Accordingly, an agreement observed in Vyakaranam et al study in 2015, in which both SBP and DBP was significantly higher in pregnant women with PE in comparison to those with normal pregnancy (P<0.05) [20] .

In this study, pregnant women with PE had significantly higher mean of serum homocysteine compared with controls (P= 0.001). Moreover, ROC curve was constructed for homocysteine level as a predictor for PE, in which cut point was 8.95 μmol/l. So, homocysteine level > 8.95 μmol/l is a predictor for PE. Homocysteine level was 90% sensitive, 87.5% specific, and 88.8% accurate in diagnosis of PE.

As compared to results of Al-Sakarneh et al study in 2021, an agreement found. They found that Serum levels of homocysteine was significantly higher in women with PE compared with controls (16.35±0.43 vs 7.25±0.21, respectively; *P*<0.001) [14]. In the same accordance, Oluwole and colleagues in a study done in 2020, found of the 167 participants, 10.8% had PE, the final analysis included 41 (24.6%) patients had a homocysteine concentration above the reference range (>15μmol/L) and 126 (75.4%) with a normal homocysteine concentration and the rate of PE was three times higher among women with high homocysteine level than those with normal homocysteine level (P= 0.01) [21].

On the other hand, results from studies investigating the relation between serum homocysteine and PE are contradictory. A case control study conducted by Shilpa et al. (2017) demonstrated significantly lower serum Hcy level in PE patients (8.90±4.33 μmol/L) compared with normal non-pregnant women (13.31±5.81 μmol/L). However, mean serum Hcy levels of the PE patients (8.90±4.33 μmol/L) were not significantly higher than those of normal pregnant women (7.52±2.25 μmol/L). The authors indicated that this insignificant minor difference in serum Hcy levels may be due to PE patients receiving folic acid supplementation during their first trimester of gestation. (P<0.05). However, mean homocysteine levels of the PE patients were not significantly higher than those of normal pregnant women (P > 0.05) [22].

Out of 40 women with PE enrolled in this study, 42.5% were with mild PE while the remaining 57.5% were with severe PE. Concerning homocysteine level in severe cases of PE in this study, pregnant women with severe PE had significantly higher mean of serum homocysteine compared to those with mild PE (P= 0.001). In consistent to other studies, a similarity was reported with a study done by Al-Sakarneh et al study in 2021, in which a strong association between the severity of PE and levels of serum homocysteine. An increase in serum homocysteine of 1 μmol/L was associated with a 3.5 mmHg increase in SBP and 1.8 mmHg

increase in DBP (P<0.05)[14]and this is also consistent with Shahbazian et al study in 2016, that involved 51 PE pregnant women, in which they reported a significantly higher serum homocysteine levels in pregnant women with severe PE compared with women with non-severe disease (P<0.05)[23]. Similarly, in Maru et al study in 2016, the association between homocysteine levels and severity of PE and complications of PE and eclampsia was confirmed as There was a direct correlation with a statistical significance in the study, of the 32 patients, 30 patients of eclampsia had an elevated level of homocysteine which is as high as 93.75 %. Of the 87 patients with elevated homocysteine levels, 81 patients had hypertension of varied severity. Si (P<0.05) [24]. A different finding observed while the current results compared to that obtained in Oluwole et al study in 2020, the final analysis of this study included 167 women; 41 (24.6%) patients had a homocysteine concentration above the reference range (>15μmol/L) and 126 (75.4%) with a normal homocysteine concentration. in which severe pre eclampsia was recorded in 7 (38.9%) of mothers with PE, moreover, no significant association was found between high homocysteine level and severity of PE (P= 0.29) [21]. Finally, our study had some limitation as the small sized sample and homocysteine level was measured at 2nd half of pregnancy when sign and symptoms of pre eclampsia have already been started.

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Nil.

Conflicts of interest:
There are no conflicts of interest**.**

CONCLUSION

1. Maternal serum homocysteine biomarker represents a non-invasive, and excellent predictor of pre-eclampsia at a cut off >8.95 μmol/l.

2. Maternal serum homocysteine is a biomarker that is also helpful to determine the severity of pre-eclampsia.

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Original article

The Relation between Chronic Viral Hepatitis B Infection and Helicobacter Pylori Infection

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Abstract:

- ***Background***: The relation between H. pylori infection and Viral Hepatitis has been subjected to substantial research in recent years, however, this relationship has not been comprehensively studied in Al Sulaymaniyah. The objective of this study is to Investigate the association between HBV infection and the H. pylori infection.
- ***Method and patient:*** A case-control study using data from 130 participants, from January 2020 to March 2021. Data is divided into two groups, a study group which consists of 65 persons of confirmed hepatitis B infection via PCR, and a control group of 65 persons with confirmed Hepatitis B negative by Hepatitis B surface antigen test, we used stool antigen test to confirm the presence or absence of H. Pylori infection in both groups.
- ***Result:*** 32% of the study group is infected with H. pylori and 15% in the control group have been tested positive for H. pylori infection. The regression analysis results reveal strong evidence that HBV infection increases the likelihood of *H.* pylori infection. This relationship is very robust and consistent even after controlling a vast number of variables as confounding and medical factors.
- ***Conclusions:*** Patients with HBV infection are more vulnerable to H. pylori infection.

- **Keywords:** H. pylori infection, HBV infection, case-control study.

INTRODUCTION

Gastric organisms were first observed more than 100 years ago and their association with gastritis has been recognized since the 1970s. In 1982, Marshall and Warren identified and cultured the gastric bacterium, *Campylobacter pyloridis*, later reclassified as *Helicobacter pylori* (hereafter *H.* pylori) [(1)]. In the case of Hepatitis, this refers to an inflammatory condition of the liver that is commonly caused by a viral infection. However, there are other potential causes of hepatitis such as autoimmune hepatitis or hepatitis that occur as a secondary result of medications, drugs, toxins, and alcohol [(2)]. The relation between *H.* pylori infection and Viral Hepatitis has been subjected to substantial research in recent years; however, this relationship has not been comprehensively studied in Al Sulaymaniyah.

The *H.* pylorus is a spiral-shaped, microaerophilic, gram-negative bacterium measuring approximately 3.5 microns in length and 0.5 microns in width. In vitro, it is a slow-growing organism that can be cultured on blood agar or selective media such as Skirrow's media incubated at 37º C in a 5 percent oxygen atmosphere for three to seven days [(3)]. While the prevalence of *H*. pylori infection is found to be very high in the developing countries - the majority of children are infected before the age of 10 and in adult's peaks at more than 80 percent before age 50 – it is relatively less in developed countries [(4)].

Previous studies indicate that the risk of *H.* pylori infection is related to socioeconomic status and living conditions early in life. Factors such as density of housing, overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher acquisition rate of *H.* pylori infection and the consumption of salted food appears to increase the possibility of persistent infection with *H.* pylori infection [(5)].

The route by which infection occurs remains unknown, however, some studies demonstrate that *person-to-person* transmission of *H.* pylori via either fecal/oral or oral/oral exposure is the most likely source of infection [(6,7)]. Additionally, contaminated water supplies in developing countries may serve as an environmental source of bacteria, for instance, children who regularly swim in rivers, streams, pools, drink stream water, or eat uncooked vegetables are more likely to be infected [(8)]. Furthermore, the iatrogenic infection has been documented following the use of a variety of inadequately disinfected gastric devices such as endoscopes and their accessories [(9)]. In addition to those suspected of being infected and being tested, gastroenterologists and nurses appear to be at increased risk for acquiring *H.* pylori due to occupational exposure to infected gastric secretions [(10)].

An infected person with *H.* pylori disease can usually be asymptomatic; however, some infected persons may have symptoms including nausea, vomiting, abdominal pain, heartburn, diarrhea, hunger in the early morning, and Halitosis [(11)].

The *H.* pylori infection is associated with many gastrointestinal diseases including peptic ulcers and malignancy such as Gastric adenocarcinoma, and Maltoma [3].

Diagnostic testing for *H.* pylori can be divided into invasive and noninvasive techniques based on the use of upper endoscopy. Endoscopy-based tests, the urea breath test and the stool antigen assay test can be used for active *H.* pylori infection. The choice of test used to diagnose *H.* pylori depends on whether a patient requires an upper endoscopy for evaluation of symptoms or surveillance, and therefore, the endoscopy is not indicated solely to establish *H.* pylori status. The choice of test depends also on other important determinants: the recent use of medications that can suppress the bacterial load of *H.* pylori (e.g., proton pump inhibitor therapy [PPI] and antibiotics), the prevalence of *H.* pylori, the test availability, and the test costs. Before applying *H.* pylori tests, both PPI and bismuth/antibiotic medication use should be stopped within one to two weeks and four weeks before testing, respectively. This is because these medications can decrease the sensitivity of all endoscopy-based tests and non-invasive tests of active *H.* pylori infection including stool antigen and urea breath test [12].

Among patients undergoing upper endoscopy, the choice of test to diagnose *H.* pylori and the type of testing varies depending on the clinical presentation and the endoscopic findings. To be able to conduct proper testing, the following points should be considered [13]:

- ❑ No active peptic ulcer bleeding
- ❑ No recent PPI/bismuth/antibiotic medications use as mentioned earlier and no indication for gastric biopsy: In patients without recent PPI/bismuth/antibiotic medication use and who do not require biopsies of the stomach for histology, the diagnosis of *H.* pylori can be established with a biopsy Rapid urease test.
- ❑ In case of recent PPI/bismuth/antibiotic medications use or indication for gastric biopsy: In patients with visible endoscopic abnormalities (e.g., gastric ulcer, gastropathy), and patients with recent antisecretory/bismuth/antibiotic use, we perform histology to diagnose *H.* pylori. Since recent PPI/bismuth/antibiotic use may diminish the numbers of bacteria detected by histology, we perform a urea breath or stool antigen assay to confirm a negative test result once these medications have been held for an appropriate length of time [14].
- ❑ Prior antibiotic treatment failures: In patients with *H.* pylori that is refractory to two courses of antibiotic therapy, we perform culture and antibiotic sensitivity testing on gastric biopsies to guide treatment.
- ❑ Active peptic ulcer bleeding: In patients with bleeding duodenal or gastric ulcer on upper endoscopy, we perform a gastric mucosal biopsy at the time of the initial endoscopy unless it is impractical or difficult such as with a blood-filled stomach. A negative biopsy result does not exclude *H.* pylori in the setting of an active upper gastrointestinal bleed, and another test (ideally a urea breath test)

should be performed to confirm a negative result [15]. If a gastric mucosal biopsy is not obtained at the time of endoscopy, we perform a urea breath test or stool antigen assay to diagnose *H.* pylori [16].

Regarding Endoscopic-based test types, the following tests are available:

1. Biopsy urease testing: The sensitivity and specificity of biopsy urease testing are approximately 90 and 95 percent, respectively [17].
2. Histology: Gastric biopsies histology can diagnose *H.* pylori infection and associated lesions, for example, atrophic gastritis, intestinal metaplasia, dysplasia, and MALT lymphoma.
3. Bacterial culture and sensitivity testing: Culturing typically is characterized as having a sensitivity greater than 90% and a specificity of 100% when performed under optimal conditions [18].

In patients who do not require endoscopic evaluation, the diagnosis of *H.* pylori should be made with a test for active infection (stool antigen assay or urea breath test). In clinical situations where patients are unable or unwilling to stop PPI therapy one to two weeks before testing, positive test results are true positives; negative results may represent false negatives and should be confirmed with repeat testing after stopping PPI therapy for one to two weeks. The noninvasive tests for the diagnosis of *H. pylori* include urea breath testing (UBT), stool antigen testing, and serology. Of these, UBT and stool antigen assay are tests of active infection. *H.* pylori serology can be positive in patients with an active or prior infection.

Noninvasive based test types include:

1. Urea breath testing (UBT): The sensitivity and specificity of UBT are approximately 88% to 95 % and 95% to 100% [19]. However, false-negative results may be observed in patients who are taking PPIs, bismuth, or antibiotics medications and in the setting of active peptic ulcer bleeding [20].
2. Stool antigen assay (SAT): The first SAT introduced was the polyclonal type and was followed by a monoclonal test. The latter test is better in both testing untreated patients and following up with treated patients [21, 22]. The detection of bacterial antigen indicates an ongoing *H.* pylori infection, and SAT can, therefore, be used to establish the initial diagnosis of *H.* pylori and to confirm eradication [17]. Among the available tests, stool antigen testing is the most cost-effective. The results from the SAT can be affected by the recent use of bismuth compounds, antibiotics, and PPIs medications.
3. Serology: The serological test can be performed via Laboratory-based - An Enzyme-Linked Immunosorbent Assay (ELISA) test - to detect Immunoglobulin G (IgG) antibodies. Although this type of testing is inexpensive and noninvasive, the guidelines recommend that serologic testing should not be used in low prevalence populations, as the low accuracy of serology would result in inappropriate treatment in significant

numbers of patients. This is because this type of testing cannot reliably distinguish between active and past infection [17, 23, 24].

4. Other infrequently invasive- and noninvasive used tests

- ❑ Polymerase chain reaction: Quantitative polymerase chain reaction (PCR) testing on gastric biopsies can be used to detect low bacterial loads. It can also be used to identify specific mutations associated with antimicrobial resistance. However, the use of PCR-based testing is limited by its high cost.
- ❑ 13C-urea assay: A serodiagnostic test using a 13C-urea assay is a noninvasive tool for diagnosis of *H.* pylori infection, but is rarely if ever, used in clinical practice. This test is performed by measuring two serum specimens; the first one is taken before ingestion and the second one 60 minutes after ingestion of a 13C-urea-rich meal. The test has a reported sensitivity of 92% to 100 % and a reported specificity of 96% to 97 % [25].

All patients with evidence of active infection with *H.* pylori should be offered treatment depending on whether there are risk factors for macrolide resistance and the presence of a penicillin allergy [26].

Chronic Viral Hepatitis B (HBV) infection

Hepatitis B Virus (HBV) infection is a global public health problem and according to the World Health Organization (WHO) about 257 million were HBV carriers in the world in 2015, and roughly 887,000 persons died the same year from HBV-related liver disease [28]. Hepatitis B viral infection can be divided into acute or chronic infection depending on the duration of infection and serological markers:

- o Acute Hepatitis B viral infection: The diagnosis of acute HBV infection is based on the detection of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core antigen (anti-HBc), with elevated alanine aminotransferase (ALT) and with a duration less than 6 months.
- o Chronic viral hepatitis B viral infection: This type is characterized by the persistence of hepatitis B surface antigen (HBsAg) for more than six months.

It is estimated that approximately two billion people worldwide have evidence of past or present infection with hepatitis B virus (HBV), and 257 million individuals are chronic carriers i.e., positive for hepatitis B surface antigen (HBsAg) [28, 29]. In 2013, viral hepatitis, primarily due to HBV and hepatitis C virus, was the seventh leading cause of death worldwide [30]. The prevalence of HBV infection varies depending upon the geographic area, and the wide range in the prevalence is largely related to differences in the age at infection time, which is inversely related to the risk of chronicity. The rate of progression from acute to chronic HBV infection is approximately 90 percent for perinatally acquired infection and in areas of low prevalence,

many of the patients who have chronic HBV were born in areas in which the prevalence is higher [31].

Hepatitis B virus (HBV) is transmitted from patients who are infected to those who are not immune i.e., hepatitis B surface antibody (anti-HBs)-negative. However, the HBV vaccination has significantly reduced the risk of transmission worldwide.

Many patients with chronic HBV are asymptomatic (unless they have decompensated cirrhosis or have extrahepatic manifestations), while others have nonspecific symptoms such as fatigue. Some patients experience exacerbations of the infection which may be asymptomatic, mimic acute hepatitis, or manifest as a hepatic failure.

Physical examination may be normal or there may be stigmata of chronic liver disease like jaundice, splenomegaly, ascites, peripheral edema, and encephalopathy may be present in patients with decompensated cirrhosis. Although the laboratory tests may appear normal, most patients would have a mild to moderate elevation in serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT). A progression to cirrhosis is suspected when there is evidence of hypersplenism (decreased white blood cell and platelet counts) or impaired hepatic synthetic function (hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia).

The extrahepatic manifestations are thought to be mediated by circulating immune complexes. It may be heralded by a serum sickness-like syndrome manifested as fever, skin rashes, arthralgia, and arthritis which usually subside with the onset of jaundice. The two major extrahepatic complications of chronic HBV are polyarteritis nodosa and glomerular disease [33].

Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection. It can be detected using an Enzyme ImmunoAssay (EIA). The HBsAg appears in serum 1 to 10 weeks after acute exposure to HBV, before the onset of clinical symptoms characteristic for acute hepatitis or elevation of serum alanine aminotransferase (ALT). In patients who subsequently recover, HBsAg usually becomes undetectable after four to six months. The persistence of HBsAg for more than six months implies chronic infection. It is estimated that less than 5 percent of immunocompetent adult patients with genuine acute hepatitis B progress to chronic infection [34]. Among patients with chronic HBV infection, the rate of clearance of HBsAg is found to be approximately 0.5 percent per year [35]. The disappearance of HBsAg is followed by the appearance of a hepatitis B surface antibody (anti-HBs). In most patients, anti-HBs persists for life, thereby conferring long-term immunity from reinfection, however, over time anti-HBs may disappear in some patients, and they may have only isolated hepatitis B core antigen (anti-HBc) IgG.

Chronic HBV infection can be divided into four different phases depending on the level of immune activity, and the type of treatment is based on the phase of the infection [36]. These phases are as follow:

1) Immune-tolerant phase: In this phase, little hepatic inflammation will be observed with normal liver tests despite elevated HBV DNA and positive HBe antigen.
2) Immune-active phase: In the next phase, there will be hepatic inflammation with liver tests, decreased DNA levels of HBV compared to the immune-tolerant phase, the ultimate loss of HBe antigen, and the appearance of HBe antibody.
3) Inactive carrier phase: This phase is characterized by normal liver tests, low HBV DNA levels, and HBe antigen-negative.
4) Reactivation phase: This phase can be recognized when patients have normal or high liver tests, high HBV DNA levels, remain HBe antigen-negative, or revert to HBe antigen-positive.

It is important to note that not all patients go through all 4 phases, and immune clearance and reactivation phases can sometimes be prolonged.

As chronic HBV infection cannot be cured, the goals of treatment are to suppress viral replication, halt the progression of liver disease, and prevent hepatocellular carcinoma. The recommended treatment timing and duration vary by the status of chronic HBV.

1) Immune-tolerant chronic hepatitis B: Most patients in this phase do not need antiviral therapy. However, antiviral therapy should be considered for patients over the age of 40 years that have a normal alanine aminotransferase (ALT) level with elevated HBV DNA (≥ 1,000,000 units/mL) and liver biopsy indicating moderate-to-severe necro-inflammation or fibrosis.
2) Immune-active chronic hepatitis B (HBeAg-negative or HBeAg-positive): In this phase, antiviral therapy is recommended to reduce the risk of liver-associated complications. The preferred drug options for initial therapy include peginterferon and nucleoside/nucleotide analogues (NAs) entecavir and tenofovir. In the case of HBeAg-positive, immune-active chronic hepatitis B with seroconversion to anti-HBe on A nucleoside analog (NA) therapy, discontinuing NA therapy after a period of treatment consolidation should be considered if there is no liver cirrhosis. However, if liver cirrhosis presents, indefinite antiviral therapy should be considered to reduce the risk of potential clinical decompensation and death unless there is a strong indication for treatment discontinuation.
3) Chronic HBV inactive carrier (Normal ALT, HBeAg negative, anti-HBe positive, HBV DNA <10,000 IU/mL and with No inflammation, variable liver fibrosis): This phase of disease does not require treatment.
4) Reactivation Phase (HBeAg negative, anti-HBe positive, HBV DNA >10,000 IU/mL, and Inflammation and fibrosis of liver): In this phase treatment with antiviral therapy should be restarted.

The aim of this study is investigating the association between HBV infection and the likelihood of *H*. pylori infection.

PATIENT and METHOD

This is a case-control study. The data is collected from the Kurdistan Center for Gastroenterology and Hepatology (KCGH) and SHAR teaching hospital in Al Sulaymaniyah at the consultant room of the admission ward. The sample consists of 130 patients over 14 months spanning from January 2020 to March 2021.

We conduct a survey that includes related questions to our study, and all patients were informed about the nature of the study and verbal consent was obtained from each of them. The data were collected randomly through face-to-face interviews over the 14 months with the patients based on a prepared questionnaire list.

The sample of the study is divided into two groups of patients:

- ❑ The first group consists of patients that are chronically infected with hepatitis B virus (study group) and includes all patients who have been diagnosed for at least 1 year with still positive HBsAg.
- ❑ The second group (control group) is randomly selected and includes those who have no known liver disease and tested negative for HBsAg.

To obtain a more accurate result, we restrict the sample by excluding the following:

- ❑ Pregnant women.
- ❑ Patients less than 18 years old.
- ❑ Patients that used protein pump inhibitors (PPIs) in the last two weeks or antibiotics in the last month, before testing for H. pylori infection.

Ethical considerations and official approvals

- ❑ Approval was taken from the scientific council of the Arab Board of Health Specialization in Iraq.
- ❑ Approval was taken from the authority of the Kurdistan Center for Gastroenterology & Hepatology (KCGH) and Shar teaching hospital in Sulaymaniyah.

- ❑ Oral informed consent was taken from each patient who enrolled in this study. Confidentiality was taken into consideration.

Statistical analysis

We applied different identification strategies to conduct this study using our sample of 130 observations. In addition to the twelve variables from the survey mentioned above, we obtained two additional variables that are essential for this study: the results from testing of both stool antigen for *H*. pylori infection and HBsAg for both study and control groups. We start by coding our information obtained from the survey and the test results using the STATA 16 statistic program.

We first conduct descriptive statistics presenting several figures and tables containing the mean and standard deviation of several variables concerning our variable of interest, *H*. pylori infection. Next, we applied *a t*-test to compare the study and the control groups where the only difference between them is whether a participant has or not an HBV infection. Third, we will be calculating and presenting the Odds ratio of this case-control study to further identify whether there is a difference between groups due to HBV infection. The advantage of these statistic tests is providing both *t*-statistics, Chi^2-statistics, and *p*-values allowing us to conclude to evaluate the difference between study- and control groups i.e., the association between *H*. pylori infection and HBV infection.

However, these three identification strategies are, in fact, not sufficient to draw any conclusion on the causal impact of HBV infection on *H*. pylori infection. Therefore, we finally conduct regression analyses to identify and quantify the relation between chronic HBV infection and *H*. pylori infection (the causal relationship). The dependent variable of our regression model (*H*. pylori) is a dummy variable that takes the value 1 if the participant has been tested positive for *H*. pylori infection and takes the value 0 otherwise. Therefore, it is not appropriate to apply the Ordinary Least Squares method (OLS) to estimate the coefficients of the independent variables in the regression models as this method requires a continuous dependent variable. Alternatively, we employ a Poisson regression approach using the maximum likelihood method to estimate our regression models to identify the relation between chronic HBV infection and *H*. pylori infection. For all statistical analyses, a *p*-value of ≤ 0.05 is regarded as statistically significant.

RESULTS

Table 1 below presents an overview of descriptive statistics for both the study and control groups. The study group indicates participants that have been tested positive for HBV infection, and control is a randomly assigned group that has been tested negative for HBV infection. The total sample size consists of 130 participants and is equally distributed among both the study

and control groups. While about 32% of the participants are infected with H. pylori bacterium in the study group (SD 5%), only 15% are infected in the control group (SD 4%). The age of participants range from 19 to 75 years old for the whole sample, and the mean age for the study and control groups is 42.26±15.21 and 39.52±14.70 years old, respectively. The gender seems to be equally distributed in which the study group consists of about 55% males and the control group includes about 52% males.

Table 1 also presents information on other confounding factors such as the residency of participants - whether they live in rural areas or the urban area of Al-Sulaymaniyah - and information on their job status. While all participants in the control group living in the city center, only 40% of the study group lives in the city center (60% lives in rural areas). The share of unemployed participants is higher in the study group, (46%) compared with the control group (38%). Only 12% of the participants in the study group were civil employees, while this category is observed to be higher among the control group (35%). The average duration for HBV infection in study group participants was approximately 5 years. Among all participants that have been diagnosed with HBV infection (study group), only 18% are taking Tenofovir medicine. Further, only 9% have a family history of other members being infected with HBV infection in the study group. Interestingly, we observe that about 52% of the study group participants have been subject to a surgical intervention where the most prevalent is Cesarean Section (C/S) with about 22% while only 15% of the participants in the control group have a history of surgery.

Table 1: General characteristics for study and control groups

	Study group (N=65) (Positive HBV infection)		Control group (N=65) (Negative HBV infection)		
	Numbers	Percentage	Numbers	Percentage	p-value
H. pylori (positive)	21	32	10	15	
Gender (male)	36	55	34	52	0.7
Occupation:					
Military-employee	7	11	3	05	
Civil employee	8	12	23	35	
Free jobs	13	20	14	22	
Unemployed	30	46	25	38	
Residency: Urban area	26	40	65	100	
Rural	39	60	0	0	
Medical factors:					
Hypertension	4	06	5	08	
D.M	1	02	5	08	

Anti-diabetic treatment	3	03	4	06
Tenofovir	12	18	0	00
On medical treatment	18	28	8	12
Past Surgical history:	34	52	10	15
Herniotomy	3	05	1	02
CS	14	22	5	08
Appendectomy	3	05	0	0
Varicocele	2	03	0	0
Family history	6	09	0	0
Social history:				
Smoker	6	09%	8	12%

Note: S.D. denotes the standard deviation of the variable. The total sample size is 130 participants. The study indicates a group that has been tested positive for HBV infection, and control is randomly an assigned group that has been tested negative for HBV infection. Each group consists of 65 participants. The data has been collected for the period from January 2020 to March 2021 from SHAR teaching hospital and Kurdistan Center for Gastroenterology and Hepatology (KCGH).

Figure 1 presents the share of patients who tested positive for H. pylori infection for both the study and control groups. About 16% of the participants that have HBV infection, i.e., the study group, have been tested positive for H. pylori infection. However, considering the control group, the proportion of H. pylori infection seems to be lower relatively with approximately 7.6%. The rest of the patients in our sample (76%) have no H. pylori infection. We can argue that the higher ratio of H. pylori infection observed in the study group could be related to the HBV infection since the only difference between the two groups is whether they are diagnosed positive for HBV infection or not.

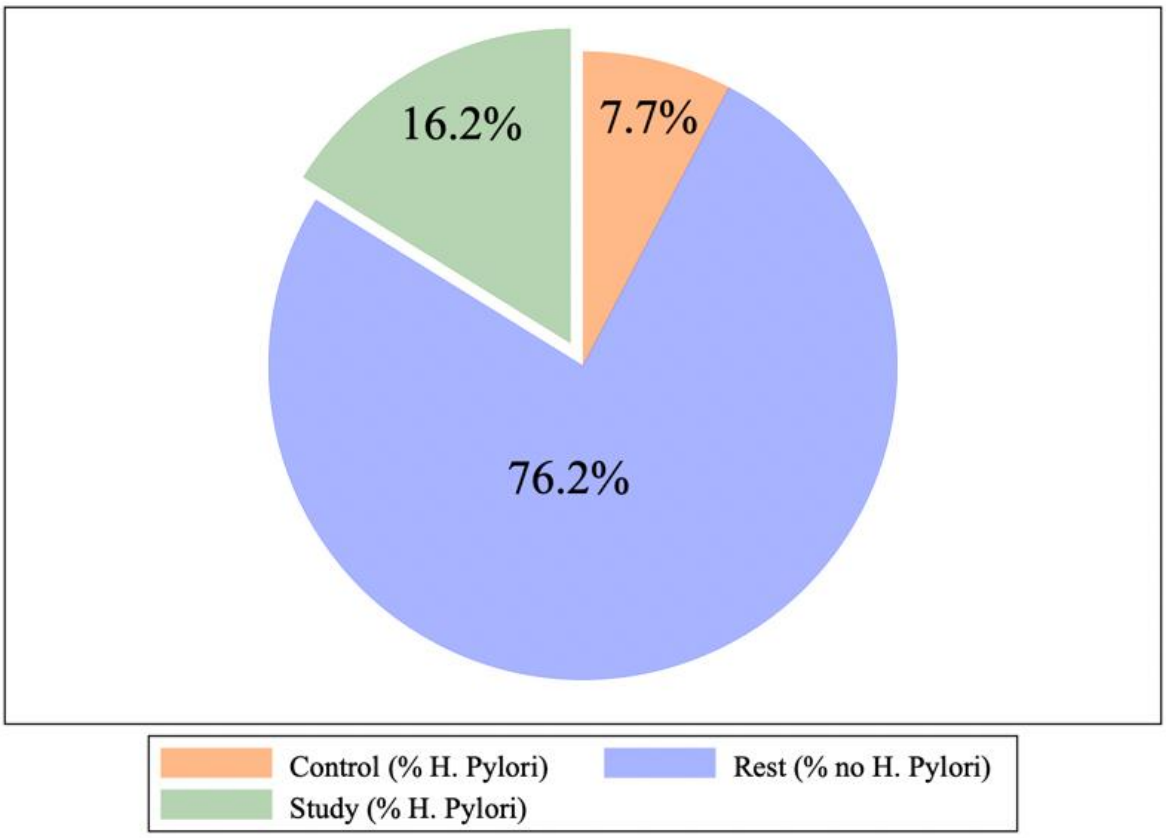


Figure 1: The distribution of patients infected with H. pylori for the whole sample

Note: Study group indicates patients tested positive for H. pylori infection and HBV. The Control group represents randomly assigned participants that have been tested negative for HBV infection.

The mean age of the participant in the study and control groups is about 42 ± 15 and 39 ± 14 years old, respectively. The small difference in mean age between the two groups is in favor of our method conducted in this study because comparing two comparable groups yield more reliable results.

Figure 2 presents the share of patients with H. pylori infection by gender. Considering the whole sample in panel A, 51.61% of H. pylori-infected patients are males and 48.39% are females. Considering the participants that have been tested positive for HBV infection (study group), 52.38% of males are infected with H. pylori and 47.62% of females are infected with H. pylori.

Panel A Panel B

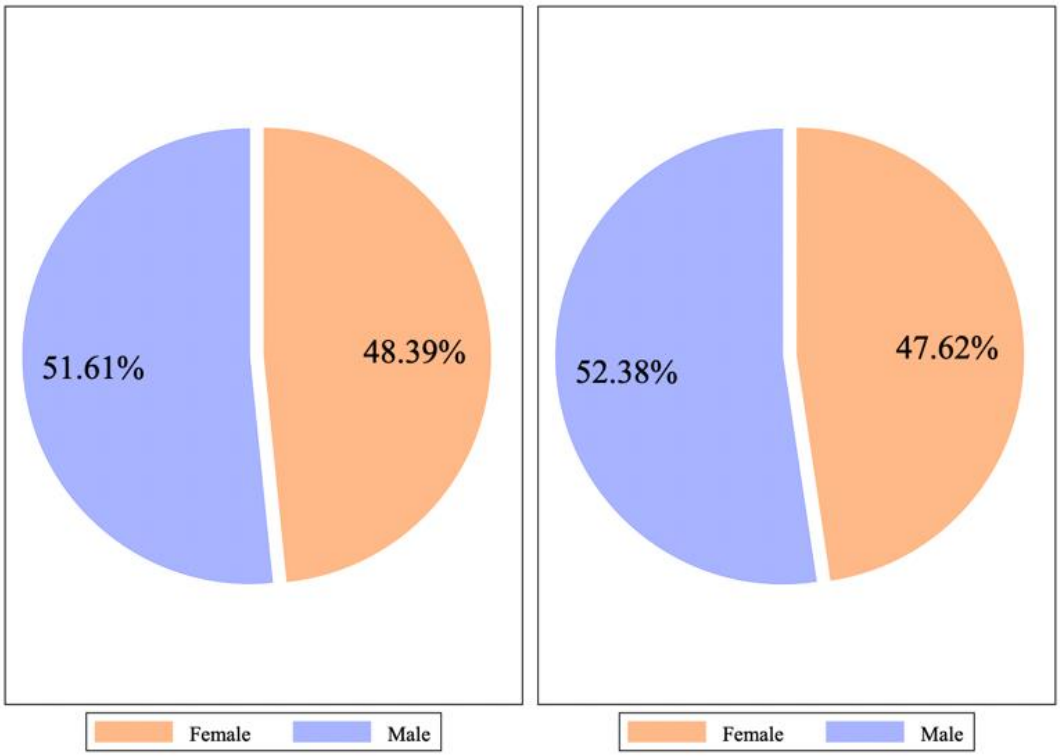
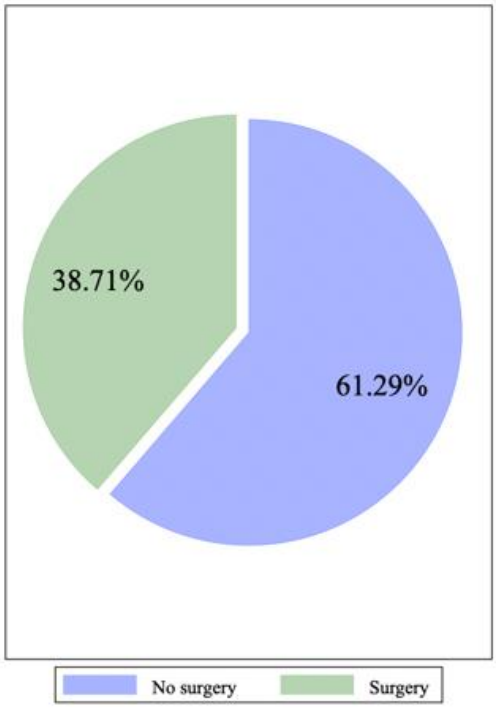


Figure 2: The distribution of patients with H. pylori infection by gender

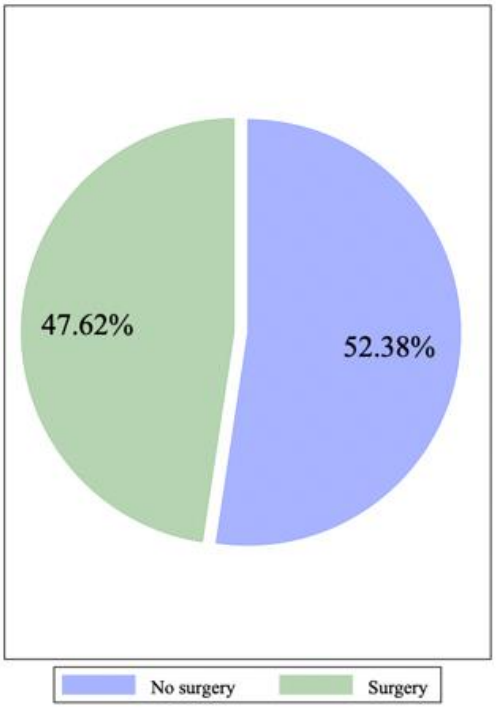
Note: Panel A presents the share of patients who tested positive for H. pylori by gender for both study and control groups (whole sample). Panel B presents the share of patients who tested positive for both H. pylori and HBV infection by gender (study group).

Figure 3 shows the patients that tested positive for H. pylori infection with previous surgical intervention for the whole sample in Panel A. About 39% of all participants have been subject to previous surgery, and about 61% had no surgical intervention. Considering the study group with HBV infection (Panel B), the share of participants with both H. pylori infection and had a surgical intervention is relatively higher (about 48%) compared with the whole sample. Panel C shows that cesarean section is the most prevalent (21.5%) among other types of surgeries. These results from Figure 3.3 may indicate a relation between previous surgical intervention and H. pylori infection prevalence. However, drawing any conclusion based on graphical presentation may be misleading; hence it is early to draw any conclusion regarding the relationship between surgical intervention and H. pylori infection before conducting any tests statistics.

Panel A



Panel B



Panel C

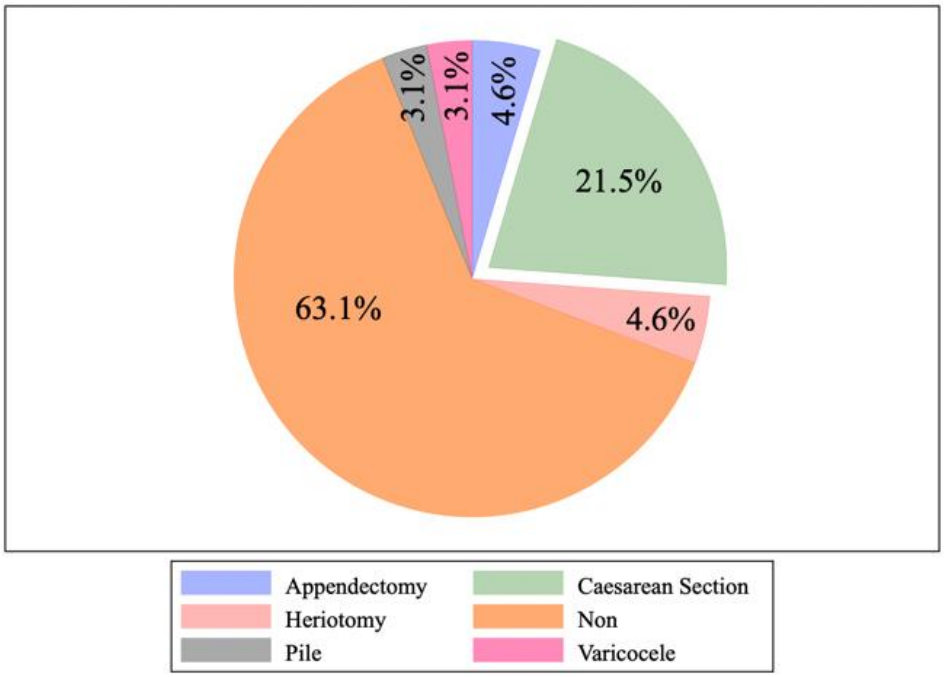


Figure 3: The distribution of H. pylori by surgical intervention

Note: Panel A shows the share of patients infected by H. pylori by surgical intervention for the whole sample (both groups). Panel B shows the share of patients with both H. pylori and HBV infection by surgical intervention (study group). Panel C presents the distribution of surgical intervention by type of surgery of patients with both H. pylori and HBV infection (study group).

T-TEST

This t-test is applied to compare the means of patients that are infected by H. pylori between two groups of patients. The study group includes patients with HBV infection while the control group includes patients that have no HBV infection. This t-test assumes that both samples are randomly assigned and that both groups have equal variance in the population.

Table 2 below shows that the overall mean of patients with H. pylori infection is 0.238, which represents the percentage of H. pylori infection patients in the whole sample (both groups). While the mean of H. pylori infection in the group that has no HBV infection is 0.154, the mean of the study group is 0.323 and the difference in means between both groups is estimated as 0.169 with a standard error equal to 0.0375.

The null hypothesis for this test is that the means are the same for both groups i.e. the difference in means between groups is equal to 0. The t-statistic of the difference in means is 2.292 with 128 degrees of freedom. Further, the p-value for the two-sided t-test is 0.0235, which is less than 0.05) significance level, indicating that the difference in means is statistically significant. Based on this we can with 95% confidence reject the null hypothesis and conclude that there is a difference in means of H. pylori infection between groups due to HBV infection.

Table 2: Two-sample t-test for patients infected with H. pylori infection with HBV infection.

Group	Obs.	Mean	Std. Err.	Std. Dev.	[95%Conf.Interval]		t-statistic	p-value
Study	65	0.3231	0.0585	0.4713	[0.2063	0.4399]		
Control	65	0.1538	0.0451	0.3636	[0.0638	0.2439]		
Combined	130	0.2385	0.0375	0.4278	[0.1642	0.3127]		
Difference		0.1692	0.0738		[0.3153	0.0231]	2 .2921	0.0235

Note: Ho: Difference = 0. Two tail t-test with 128 degrees of freedom. Study and control groups contain information on patients that have Hepatitis B and patients that have not Hepatitis B, respectively.

We also applied the Two-sample t-test to compare means by gender and age concerning H. pylori, presented in Table 3 below. The p-value of 0.77 is greater than the significance level of 5% (0.05) indicating that gender has no relationship with H. pylori infection.

Table 3: Two-sample *t*-test for patients infected with *H*. pylori infection concerning gender (by sex)

Gender	Obs.	Mean	Std. Err.	Std. Dev.	[95%Conf.	Interval]	t statistic	p-value
Female	60	0.25	0.056	0.44	[0.14	0.36]		
Male	70	0.23	0.057	0.42	[0.13	0.33]		
Combined	130	0.24	0.038	0.43	[0.16	0.31]		
Difference		0.02	0.076		[-0.13	0.17]	0.284	0.777

In Table 4 below we applied the t-test for patients infected with H. pylori concerning age. However, the p-value is 0.851 which is greater than the significance level of (0.05) provides evidence that H. pylori infection is not associated with the age of the participants.

Table 4: Two-sample t-test for patients infected with H. pylori infection concerning age (by age)

H. pylori	Obs.	Mean	Std. Err.	Std. Dev.	[95%Conf.	Interval]	t statistic	p-value
Negative	99	41.03	1.47	14.64	[38.11	43.95]		
Positive	31	40.45	2.91	16.19	[34.51	46.39]		
Combined	130	40.89	1.31	14.96	[38.30	43.49]		
Difference		0.58	3.09		[-5.54	6.69]	0.187	0.851

Note: Ho: Difference = 0. Two tail t-test with 128 degrees of freedom.

THE ODDS RATIO

Table 5 shows the results of the odds ratio with the Chi^2 test for the null hypothesis that there is no difference in the odds between the study and control groups, i.e. the odds are equal to 1 (no association between HBV infection and H. pylori infection). Table 5 shows that 21 participants in the study group that have positive HBV infection – have positive H. PYLORI infection and 44 participants are tested negative for H. pylori.

Considering the control group, 10 participants have positive H. pylori infection and 55 of the participants have no H. pylori infection. The total share of H. pylori infections among all

participants in both groups is 24%. The p-value (0.02) from the Chi^2 test is less than 5% (0.05) significance level suggesting that we can reject the null hypothesis. Further, the odds ratio is 2.6 which is greater than 1, indicating that the HBV infection might be a risk factor for the H. pylori infection. The magnitude of the odds ratio – the strength of the association – is above 1 which indicated that the relationship between HBV infection and H. pylori infection is likely causal.

Table 5: The Odd ratio and Chi2 test of the association between HBV and H. pylori infection

	H. pylori (Positive)	H. pylori (Negative)	Total	Share H. pylori (Positive)
Study (Positive HBV)	21	44	65	32%
Control (Negative HBV)	10	55	65	15%
Total	31	99	130	24%
	Point estimate		[95% Conf. Interval]	
Odds ratio	**2.63**		**[1.05**	**6.88]**
Chi^2	5.13			
P-value	0.02			

Note: Chi^2 denotes the Chi-squared test to test the association between HBV and H. pylori infection. Ho: Odds = 1. Study and control groups contain information on patients that have Hepatitis B and patients that have not Hepatitis B, respectively.

POISSON REGRESSION RESULTS

The results from the descriptive statistics, the t-test, and the odds ratio test are not sufficient to provide evidence on the relation between H. pylori infection and HBV infection as the aim of this study is to identify this relationship. We, therefore, conduct a Poisson regression to be able to conclude this relationship.

We first regress the dummy variable H. pylori on the dummy variable that takes the value 1 if the study group - tested positive for HBV infection- and takes the value 0 if the control group. The results present in Table 6 below demonstrate that the coefficient on the variable Group (HBV) is positively significant (p-value < 0.05) indicating that there is a relation between H. pylori and HBV infection. The result can be interpreted as the likelihood of having H. pylori infection higher if a patient tested positive for HBV infection.

Table 6: Poisson regression results without control variables

	Coef.	Robust Std. Err.	Z-statistics	P-value	[95% conf. Interval]
Groups (HBV)	0.74	0.34	2.16	0.03	[0.06 1.41]
Constant	-1.87	0.29	- 6.41	0.00	[-2.44 -1.30]
Observation	130				

Note: The dependent variable is H. pylori infection, which is a dummy that takes the value 1 if the participant tested positive for H. pylori infection and 0 otherwise. Groups (HBV) is a dummy that takes the value 1 if the participant tested positive for HBV infection (study group) and 0 otherwise. We use a 5% significance level, and we use STATA 16 to produce the results. The standard errors reported are robust for heteroskedasticity.

Table 6 above provided evidence on the relation between H. pylori and HBV infection; we include confounding factors in the second regression presented in Table 7 below to check the robustness and the consistency of the coefficient on the Group (HBV). The confounding factors include age, gender, job status, whether the participant is a smoker or not, and the residency of the patients. The coefficients of these variables are, however, non-significant as the p-values are higher than the significance level of 5%. This indicates that, for example, being a man or woman, or living in the city center or the rural area of Al Sulaymaniyah or age has no relation with the likelihood of being infected with H. pylori. These results are not reported, but we reported only the coefficient of the Group (HBV) that is even after controlling for these additional factors is still significant at the 5% level. We notice that the magnitude of the coefficient increases after including these confounding factors (from 0.74 to 1.05).

Table 7: Poisson regression results after controlling for confounding factors.

	Coef.	Robust Std. Err.	Z-statistics	P-value	[95% conf. Interval]
Groups (HBV)	1.05	0.40	2.62	0.01	[0.26 1.84]
Constant	- 2.05	1.00	- 2.04	0.04	[- 4.01 - 0.08]
Observation	130				

Note: The dependent variable is H. pylori infection, which is a dummy that takes the value 1 if the participant tested positive for H. pylori infection and 0 otherwise. Groups (HBV) is a dummy that takes the value 1 if the participant tested positive for HBV infection (study group) and 0 otherwise. The confounding factors include age, gender, job status, whether the participant is a smoker or not, and participant residency. The confounding factors are included in the Poisson regression but not reported in the table. A table of all results can be provided upon request. We use a 5% significance level, and we use STATA 16 to produce the results. The standard errors reported are robust for heteroskedasticity.

In addition to the confounding factors, we lastly include some medical factors to evaluate and check the consistency of the coefficient of the Group (HBV). We reported only the significant

coefficient in Table 8 below. The coefficient of the variable Anti-HTN drugs is positive and significant at a 5% level (p-value 0.00), indicating that a patient with hypertension on a regular medication is less likely to be infected with H. pylori infection.

A growing body of evidence suggests that H. pylori infection is associated with diabetes and may cause insulin resistance. H. pylori-induced gastritis can also potentially affect the secretion of gastric-related hormones and inflammatory cytokines. The coefficient of Diabetes Mellitus (D.M) in Table 8 is positively significant at a 5% level (p-value =0.00) indicating that patients with D.M are more likely to be infected by H. pylori infection. However, being on regular medication (oral hypoglycemic drugs and insulin) decreases the likelihood of H. pylori infection, as shown in Table 8 that the coefficient of the variable D.M medications is negatively significant at a 5% level (p-value =0.00).

The results from Table 8 also provide evidence that among patients with surgical intervention in the participants of our study, Varicocele surgery is negatively associated with H. pylori infection. The viral copies coefficient is positively significant at a 5% level (p-value =0.01), indicating that the higher the Viral copies the higher is the likelihood of H. pylori infection.

Table 8: Poisson regression results after controlling for both confounding and medical factors

	Coef.	Robust Std. Err.	Z-statistics	P-value	[95% conf. Interval]
Groups (HBV)	1.34	0.57	2.35	0.02	[0.22 2.45]
Anti-HTN drugs	-16.25	1.19	-13.58	0.00	[-18.60 -13.90]
D.M	17.36	0.98	17.72	0.00	[15.44 19.28]
D.M medications	-16.33	1.19	-13.76	0.00	[-18.65 -14.00]
Varicocele	-15.75	0.88	-18.00	0.00	[-17.47 -14.04]
Viral copies	9.91e-09	4.02e-09	2.47	0.01	[2.03e-09 1.78e-08]
Constant	-2.11	0.75	-2.80	0.01	[-3.59 -0.63]
Observation	130				

Note: The dependent variable is H. pylori infection, which is a dummy that takes the value 1 if the participant tested positive for H. pylori infection and 0 otherwise. Groups (HBV) is a dummy that takes the value 1 if the participant tested positive for HBV infection (study group) and 0 otherwise. The confounding factors include age, gender, job status, whether the participant is a smoker or not, and participant residency. Additionally, we include medical factors in the regression. Both the medical and the confounding factors are included in the Poisson regression but not reported in the table. A table of all results can be provided upon request. Anti-HTN drugs refer to antihypertensive drugs and D.M medications refer to oral hypoglycemic drugs and insulin. We use a 5% significance level, and we use STATA 16 to produce the results. The standard errors reported are robust for heteroskedasticity.

Considering our variable of interest, Group (HBV), we observe that even after controlling for a vast number of variables, the relation reflected in the significant coefficient is still robust and consistent. The sign of the coefficient is positive in all three regressions (Table 6, 7, and 8), and

the p-value is also less than 0.05. This provides strong evidence allowing us to conclude that HBV infection increases the likelihood of H. pylori infection.

DISCUSSION

The relation between *H.* pylori infection and Viral Hepatitis has been subjected to substantial research in recent years; however, this relationship has not been comprehensively studied in Al Sulaymaniyah. In this study, we applied different identification strategies attempting to conclude the relationship between H. pylori and HBV infection. The total sample size consists of 130 participants and is equally distributed among both the study and control groups. In the study group, 32% of participants are infected with *H.* pylori (SD is approximately 5%), and only 15% of the patients are infected with *H.* pylori in the control group (SD is approximately 4%). The age of participants ranges from 19 to 75 years old for the whole sample, and the average age for the study and control groups were comparable. The gender seems to be equally distributed in which the study group consists of about 55% males and the control group includes about 52% males.

The results indicate that patients that are tested positive for HBV infection have a high probability of being infected by H. pylori. Our finding is following the literature and adds important findings to the existing few studies on the relation between *H.* pylori infection and HBV infection. A similar study was done by Fan et al in 1998. This study concludes that of the 96 patients with hepatitis B, 55 (57.3%) were positive for serum IgG anti-*H.* pylori, significantly greater than in the control group of 104, where 44 (42.3%) were positive ($P < 0.05$) [37].

A study published in 2016 by Wang J et al, showed that *H.* pylori infection may increase the risk of progression of chronic HBV infection among the Chinese population [38].

Patents on regular Anti-HTN drugs are less likely to be infected with *H.* pylori infection, as shown in the results of our study, and the relation between hypertension and H. pylori infection has been subjected to many studies in the last year, for example, a study done by Migneco A et al in 2003, pointed out a significant decrease in blood pressure values, in particular, in diastolic blood pressure values, after *H.* pylori eradication in hypertensive patients [39]. Another study done by Xiong et al in 2020 showed that *H.* pylori infection was positively associated with the prevalence of hypertension [40].

Furthermore, an Egyptian study was done by Mohammed AA et al in 2018 about the association between severity of liver disease, frequency of *H.* pylori Infection, and degree of gastric lesion in patients with HBV infection. This study provided evidence that *H.* pylori antigen in stool was detected in 45.7% of the control group (healthy group), and a higher percentage (60%) was

detected in the patients' group (known case of chronic HBV infection) [41]. In our study there was a significant relationship between H. pylori infection and diabetes, this result is consistent with the literature on the relation between D.M and *H.* pylori done by Kayar et al in 2015 [42].

We have found in our study that the higher the Viral copies the higher is the likelihood of H. pylori infection, this relation has been a subject to some studies previously and our result is consistent with the literature done by Haung et al in 2017 [43].

One potential limitation of this study could be the relatively small sample size. Further research on this topic is recommended to use a larger sample size and include more variables for the patient's medical history and socioeconomic factors.

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There are no conflicts of interest**.**

CONCLUSION

- The mean age of the participant in the study and control groups is about 42 ± 15 and 39 ± 14 years old, respectively.
- The prevalence of H. Pylori infection is about 32% in patients with HBV infection, but it is only 15% in the control group.
- HBV infection increases the likelihood of H. pylori infection.
- Age and gender were not associated with an increase in the incidence of H. pylori infection.

RECOMMENDATIONS

Based on the findings from this study, we suggest that any patients with positive HBV infection are recommended to be tested for *H.* pylori infection.

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Original article

Correlation between HbA1c and lipid profile in patients with Type2 diabetes mellitus

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Abstract:

- ***Background***: Diabetes mellitus is one of the greatest health threats of recent times for global population, T2DM is associated with two to four excess risk of cardiovascular disease, Serum lipids are frequently abnormal and are likely to contribute to the risk of coronary artery disease, and there an 18% increased risk of cardiovascular disease for each 1% increase of HbA1c in diabetic population,
- ***Method and patient:*** this is across sectional study which was carried out on 100 diabetic patients ,62 male and 38 female with age from 38-75years, after fasting of at least 8 hours, fasting blood sugar, HbA1C and lipid profile were measured.
- ***Result:*** patients were divided into two groups; the controlled group with HbA1c of 7% or less, and uncontrolled group with HbA1c of more than 7% ,the controlled group include 28% of the patients while the uncontrolled group include 72% of the patients with mean age of 50.50±12.60 and 53.94±7.99 respectively, with no significant difference(p-value=0.187), while there was significant difference in lipid profile between the two groups.
- ***Conclusions:*** most diabetic patients are uncontrolled and dyslipidemia, and HbA1c is used as a dual marker for dyslipidemia and diabetic control.
- **Keywords:** Type 2 DM, HbA1c, Dyslipidemia

INTRODUCTION

American Diabetes Association (ADA) proposed the use of HbA1c in the definition of diabetes and the category of increased diabetes risk (which also includes impaired fasting glucose and impaired glucose tolerance [1]. Diabetes is one of the biggest health threats of recent times for the global population, rich and poor alike. It was estimated that, in the year 2017, more than 425 million people globally were suffering from diabetes.

The burden is increasing, predominantly in low- and middle-income countries, where about 80% of total diabetes deaths in the world occur [2]. T2DM is associated with significant long-term complications, particularly vascular disease. It has been reported that T2DM is associated with a two-to fourfold excess risk of cardiovascular disease (CVD) [3]. Although the prevalence of both type 1 and type 2 DM is going to increase, type 2 DM is expected to rise more rapidly in future because of increased obesity and reduced activity levels [4]. Serum lipids are frequently abnormal and are likely to contribute to the risk of coronary artery disease, worsening of glycemic control deteriorates lipid and lipoprotein abnormalities and particularly of diabetes mellitus. The American Diabetes study (ADA) has designated HbA1c level of <7% as a goal of optimal blood glucose control and the American Association of Clinical Endocrinologist has further recommended HbA1c level of <6.5% . Criteria for abnormal lipid profiles were based on the ADA criteria, Hypercholesterolemia refers to a total cholesterol level ≥ 200 mg/dl, Hypertriglyceridemia refers to a level is ≥ 150 mg/dl, HDL was considered low when the level is < 40 mg/dl in males and < 50 mg/dl in females, LDL was considered high when the level is ≥ 100 mg/dl. Dyslipidemia was defined as the presence of one or more of the previous abnormalities in serum lipids [5]. The higher prevalence of lipid abnormalities in diabetes mellitus has been attributed to insulin resistance or deficiency that affects key enzymes and pathways in lipid metabolism, So, hyperglycemia, dyslipidemia and coronary artery disease relate well with each other in type 2 diabetes and it has been proposed that higher prevalence of cardiovascular disease in type 2 diabetes is due to chronic uncontrolled hyperglycemia, and hence strict control of hyperglycemia and dyslipidemia can be preventive [6]. Patients with diabetes can have a reasonably normal lifestyle if they are well educated and motivated concerning the disease, Intensive treatment strategies have been demonstrated to reduce complications in diabetics [7]. there is an 18% increased risk of CVD for each 1% rise in absolute HbA1c levels in the diabetic population. This positive correlation between HbA1c and CVD has been demonstrated in nondiabetic cases, even within the normal range of HbA1c [8]. The aim of this cross-sectional study is to know the relation of HbA1c to lipid abnormalities in patient with T2DM.

PATIENT and METHOD

This is across sectional study in which a total of one hundred patients , 62 male and 38 female were included, and was carried out in K-1 hospital, north oil company, Kirkuk city in Iraq, with age from 38 to 75year,in the period from June to September 2021, after fasting of at least 8hours, fasting blood sugar, HbA1C, Cholesterol ,Triglyceride, LDL and HDL were measured, patients were diagnosed as type 2 diabetic as per American Diabetes Association guidelines 2022 or already taking treatment for type 2 diabetes, dyslipidemia was defined by presence of one or more than one abnormal serum lipid value, Controlled diabetes mellitus is considered as HbA1c =7%or less and uncontrolled diabetes HbA1c of more than 7%, Criteria for abnormal lipid profiles were based on the ADA criteria, S.LDL was measured by Friedewald Equation;(LDL=Total cholesterol-Triglyceride/5-HDL).

Descriptive statistics were reported using mean with standard deviation (SD) for numerical data, and relative frequencies (percentages) for categorical data, the statistical data were analyzed by SPSS version 26, a p-value of less than 0.05 was regarded as significant.

RESULTS

This study included 100 patients with type 2 diabetes ,72 male and 28 female with age from 38 to 75 yrs,1n which(table -1) illustrate two groups of patients, the controlled group with HbA1c of 7% or less, and the uncontrolled group with HbA1c of more than 7%,the controlled group include 28% of the patients while the uncontrolled group include 72% of the patients, the mean age of controlled group was 50.50 ± 12.60,while the mean age of uncontrolled group was 53.94 ± 7.99 ,with no significant difference between the two groups(p-value=0.187), while there was significant difference in fasting blood sugar, Cholesterol, Triglyceride, LDL, HDL and Cholesterol/HDL-C ratio between controlled and uncontrolled group **Table 1**.

Table 1. Illustrates parameters in controlled and uncontrolled diabetic groups.

Parameter	HbA1c =7%or less	HbA1c >7%	P-value
Age (Years)	50.50±12.60	53.94±7.99	0.187
Fasting Sugar (FBS)	144.39±59.75	185.11±82.34	0.007 *
S. cholesterol	179.89±24.71	202.74±55.45	0.006 *
S. triglyceride	162.66±39.77	216.43±153.50	0.007 *
S.LDL	94.92±29.68	118.14±42.28	0.003 *
S.HDL	41.88±9.74	34.90±6.11	0.001*
Cholesterol/HDL	4.58±1.41	5.50±2.28	0.018 *

** Significant P<0.05*

DISCUSSION

HbA1C is the main indicator of diabetes control in the previous 6-8 weeks, in addition there is significant correlation between diabetic control and lipid profile in T2DM, and HbA1C as well as lipid profile are significantly correlated with cardiovascular complications of Type 2 DM, so HbA1C can be used as a dual marker of diabetic control and dyslipidemia in type 2 diabetes mellitus [(9)]. Dyslipidemia is prevalent in diabetes mellitus because insulin resistance or deficiency affects key enzymes as well as pathways in lipid metabolism, and the following processes are affected: apoprotein production, regulation of enzyme lipase, action of cholesterol ester, the transfer proteins and the hepatic and peripheral actions of insulin .Even more, it has been proposed that composition of the lipid particles in diabetic dyslipidemia is more atherogenic than other forms of dyslipidemia, this means that even normal lipid concentrations could be more atherogenic in diabetic than nondiabetic people. In our study there was no significant difference in mean age of controlled and uncontrolled group, while the values of FBS and lipid concentrations in controlled diabetic was significantly less than those in uncontrolled group, in addition, in our study 72% of patients had dyslipidemia, these findings are correlated with other studies:

Gligor Romana, et all study showed that HbA1c is a good predictor of triglyceride, cholesterol, LDL and HDL, and that HDL cholesterol is inversely, and non HDL cholesterol directly, correlated with coronary heart disease (CHD) risk in diabetes mellitus [(11)].

In studies from Saudi Arabia, Jordan, and Kuwait 73%, 65.1%, and 66.7% of patients respectively had poor diabetic control. Similar figures had noted in studies conducted in UK, and dyslipidemia is more frequent in poorly controlled diabetes compared to diabetes with good glycemic control [12].

Kameran Hassan Ismail demonstrated that there is significant difference of total cholesterol, triglycerides, and LDL cholesterol between controlled and uncontrolled diabetes mellitus [13].

Emina Panjeta, et all study showed that dyslipidemia is correlated with atherosclerosis, and up to 97% of diabetic patients are dyslipidemia and the severity of dyslipidemia increases in patients of higher HbA1c value [14].

It was observed that main lipid predictor of vascular events was mean TC/HDL-C ratio with the aim to use this ratio as a guide for treatment of diabetic patients with dyslipidemia and it is worth to state that apo-B containing particles and small LDL-C particles are significantly increased in diabetes and these metabolic markers are indirectly reflected by TC/HDL-C ratio more than LDL-C alone. The significant association between HbA1c with TC/HDL-C ratio suggests that improved lipid status reflects good diabetic control [15].

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Nil.

Conflicts of interest:

There are no conflicts of interest**.**

CONCLUSION

Most diabetic patients are uncontrolled and are dyslipidemia, HbA1C is used as a dual marker for glycemic control as well as dyslipidemia, which both are main causes of cardiovascular complications of diabetes, and good glycemic control lead to improved lipid state and less diabetic complications.

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Original article

Spontaneous Correction of Extreme Degree Femur Ante –Version in Developmental Dysplasia of the Hip

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Abstract:

- ***Background***: Developmental Dysplasia of the hip is common problem, both severe acetabular dysplasia and proximal femoral ante-version are the main pathology that should be managed as early as possible. Treatment of Developmental Dysplasia of the hip (DDH) should be commenced after delivery, during infancy and in very young children because maximum potential for development and remodeling of the acetabulum and proximal femur were encountered up to the age of 4 years. Surgical correction of idiopathic developmental dysplasia of the hip (DDH) is one of the most challenging problems in pediatric orthopedic surgery.
- ***Method and patient:*** Between June 1994 and December 2018, a total of 626 hips with Developmental Dysplasia were treated according to their age at presentation.
- ***Result:*** In 110 hips (out of the total 132 hips, underwent surgery) treated by open reduction with or without salter innominate osteotomy, the following results were achieved: A – In all these cases , there was severe degree of femoral ante-version (Intra-operative evaluation) and this was found in 100% of the patients with developmental dysplasia (DDH)**,** especially in those children above 2 years of age. B – Open reduction with Salter Innominate Osteotomy gave excellent results in 72 hips within the age group 18 month-2.5 years. There was no indication for femoral shortening to be performed in these patients – All these hips showed spontaneous correction of extreme degree of femoral ante-version, this was seen in all patients underwent open reduction with or without Salter Osteotomy and there was no need for Derotation Osteotomy in all these children with developmental dysplasia of the hip (DDH) in the age group 18 months-2.5 years.

- ***Conclusions:*** In all children with developmental dysplasia of the hip younger than 2.5 years of age, there will be spontaneous correction of femoral ante-version and there was no indication for de-rotational osteotomy of the proximal femur even in extreme degree of femoral ante-version.
- **Keywords:** Developmental Dysplasia of the hip, femoral Ante-Version, salter Innominate osteotomy.

INTRODUCTION

The choice of treatment for DDH is age- dependent. It is believed that in DDH, if the treatment is not started before weight-bearing, the prognosis is poor for the satisfactory development of hip joint.

The treatment goal is to achieve a stable, congruent, and concentric hip joint as early as possible, which in turn will preclude or postpone the development of degenerative osteoarthritis (OA) of the hip [1-4].

In general, for children up to 12–18 months, though open reduction (OR) may be needed to get a concentric reduction, pelvic osteotomy (PO) is rarely required considering remodeling potential [5-9]. Between 18 months to 4 years, the need for a PO at the time of OR is controversial (10, 11, 12). However, Salter and Pemberton strongly believed in adding the acetabular procedure at the time of primary treatment to maximize the likelihood of normal acetabular development [13,14].

As the child growing older, different surgical intervention will be essential for treatment. Re-directional and reshaping Osteotomy of the acetabulum (salter -1961 or Pemberton – 1965) will be required, in addition to open reduction to encourage development and remodeling of the dysplastic acetabulum and to obtain coverage and containment of the capital femoral epiphysis [15-17].

Pemberton stated that the 'structural defect in the anterior acetabulum is a constant finding in DDH, and surgical correction of dysplasia should include correction of this defect.

Until infancy, concentric reduction of the femoral head into the acetabulum through closed or open methods is generally sufficient to get reciprocal remodeling to achieve a stable and congruent hip. Past infancy, most surgeons agree that treatment with a pelvic osteotomy (PO), with or without a femoral osteotomy (FO), is indicated to ensure adequate femoral head coverage [18-20].

Femoral shortening (klisic and jankovic – 1976) is another important procedure in the treatment of older children with DDH [21-23].

The aim of this study was to confirm that Spontaneous correction of severe degree of proximal femoral ante –version was possible in children younger than 2.5 years of age without surgery.

PATIENT and METHOD

In this study a total of 626 hips with developmental dysplasia was presented in 401 patients, it was bilateral D. D. H in 225 patients (56.10 %) and unilateral in 176 patients (43. 9 %), 236 patients were female (59 %) and 165 patients were male (41 %) with developmental dysplasia of the hip .

These patients were collected and treated from June 1994 to December 2018 in Two Teaching Governmental Hospitals (Kirkuk & Erbil) because congenital dislocation of the hip is very common in this province.

These cases were arranged according to the age to the following groups:

1 – Total N0. of 494 hips in 298 patients (196 bilateral, 102 unilateral) were treated non – operatively and arranged as follows:

Group A:

included 352 hips in patients aged from < 1 month till 3 months, were treated by pavlik harness brace or plaster spica for 2 – 3 months (the hips should be protected in about 100 – 110 degrees flexion & around 50 – 60 degrees abduction.

Group B:

included 142 hips in patients from the age > 3 months till 18 months, treated as follows: in younger children, directly under general anesthesia , both hip should be gently reduced , then plaster spica cast was applied (with or without adductor tenotomy) , post-operative checking x-ray was mandatory in every case to confirm the reduced position and the containment of the hips in plaster spica .

Always those hips with adductor tenotomy showed better outcome than those without tenotomy.

Plaster spica was applied for 2—3 months until growth and remodeling of the osseus acetabular roof was obvious on follow-up x-ray films.

In 12 patients with bilateral D. D. H and because of persistent acetabular dysplasia, after removal of the plaster spica it was followed by another Batchler plaster cast for about.

4 - 6 weeks period.

Checking x-ray monthly was taken during follow –up.

In older children, at the start of treatment and on admission to the Hospital, skin traction was applied to the lower limb on gradual abduction frame for about 10 days, was found to be very beneficial.

Failure of conservative treatment, open reduction should be performed once containment and concentric reduction of the hip was not achieved at the start with closed method.

2 – The following groups included a total of 132 hips in 103 patients (29 bilateral, 74 unilateral) were treated operatively and arranged as follows:

Group A:

included 110 hips ranged between 12 months-2.5 years old, 38 hips were treated by open reduction alone, provided that the acetabulum was not dysplastic, and reduction was stable.

In the remaining 72 hips open reduction with salter innominate osteotomy of the iliac bone were performed, were manipulated as follows:

In all hips treated surgically, severe proximal femoral ante-version was encountered (which was very clearly observed per-operatively because once the capsule opened the femoral head was looking and pointing to the ceiling) which indicate severe ante-version (up to 90 degrees) and to keep the femoral head stable and well contained inside the acetabulum , the limb must be in extreme position of internal rotation .

This position of internal rotation was maintained in plaster spica cast post-operatively for two – three months , in few cases , this plaster spica is replaced and followed by cross – bar plaster involving the both legs only (broomstick plaster) for about 4 - 6 weeks , thus the hip region is free (above knee plaster with the limb in abduction and internal rotation) thus allowing and encouraging sitting and lying exercises (flexion and extension of the hip) , gradually ante-version will be corrected and the limb will be in neutral position .

Checking x-ray monthly was ordered to check containment, the growth, development and remodeling of the osseous acetabular roof and the growth and remodeling of proximal femoral epiphysis.

These 110 hips showed spontaneous correction of femoral ante-version. All these cases had complete correction of extreme degree of femoral.

iante-version without any surgery.

SURGERY

Regarding the surgical procedure, the hip was approached anteriorly through ilio-femoral incision (smith – Petersen). Gluteus medius, G. minimus, tensor facia lata and abdominal muscles must be stripped subperiosteally from outer and inner surfaces of the iliac bone to the greater sciatic notch specially if acetabuloplasty was decided.

The dissection was carried more medially by dividing both heads of rectus femoris muscle to get access to the acetabulum, therefore anatomical landmarks like the anterior superior iliac

spine, anterior inferior iliac spine and the greater sciatic notch, all must be clearly seen in the operative field in front of the surgeon.

Kirschner wires were used to secure the bone graft which was used in performing salter innominate osteotomy. During surgery division of lliopsoas tendon at insertion to the lesser trochanter was done, division of transverse ligament of the acetabulum and capsulorraphy were performed in all patients.

Once the femoral head was reduced into the acetabulum, reduction must be easy without using force to avoid risk of avascular necrosis of the capital femoral epiphysis, reducing the femoral head by force is the main cause of failure of surgery directly in the follow-up period and the hip will subluxate or even frankly dislocate.

The surgeon must be very meticulous in dissection and respect anatomy of each muscle, tissue planes and protect the main neuro-vascular structures during dissection. Protect the blood supply around the proximal femur (tributaries of medial and lateral circumflex femoral artery) to minimize the risk of avascular necrosis of the femoral epiphysis and to avoid tissue necrosis.

Bad surgical technique and forcible reduction of the femoral head are the main causes of post-operative stiff hip and avascular necrosis of the proximal femoral epiphysis.

Group B: included 22 hips with unilateral DDH aged 3 years to 4 years, were treated by open reduction with sub-trochanteric osteotomy (shortening, varus, and derotational osteotomy) , femoral shortening was very necessary to reduce pressure on the hip and to avoid reduction by force , in all cases salter innominate osteotomy was done at the same time .

RESULTS

In majority of patients treated for DDH, the only possible follow-up of these patients was by keeping the family in contact during the period of treatment in plaster and until ambulation.

The common cause of failure in treatment of DDH in children was improper plaster spica application and poor family compliance during follow up.

The criteria for success are:

1- Containment and concentric reduction of the femoral head inside the acetabulum on plain radiology or CT imaging and subsequent checking x-rays in the period of follow-up.
2- During the period of follow-up, the growth and appearance of the ossifying nucleus center in the cartilaginous capital femoral epiphysis is another good prognostic sign.

3- After a period of 2—4 months (rarely up to 6 months) ossification of the hyaline cartilage, growth and the development of the bony acetabular roof should be obtained and the dysplastic acetabulum must be replaced by well-formed bony roof with acetabular index should be < 25° (Hilgenreiner's line and a line from a point on the lateral triradiate cartilage to a point on lateral margin of acetabulum) .
4- Developmental dysplasia of the hip cause delayed walking and once the child was treated and the femoral head stable and well contained in the acetabulum, the patient can put body weight on the limb and start walking.
5- The remodeling of the shaft – neck angle from the coax – valgus position to be around 120 – 130 degrees, is another indication for remodeling of proximal femur.
6- Recurrence of the dislocation was never recorded in the following years until adult life because once containment of the femoral head and developmental of the osseous acetabular roof were achieved within the period of treatment which usually takes 3—6 months after surgery, this indicate normal stable hip joint and there is no chance of recurrence in future.

Complication like avascular necrosis of proximal femoral epiphysis was seen in two hips treated conservatively only (may be due to prolonged plaster spica application or forcible reduction).
Joint stiffness and deep seated wound infection were not seen.
Avascular necrosis of proximal femoral epiphysis was not happened in surgically treated patients with DDH.

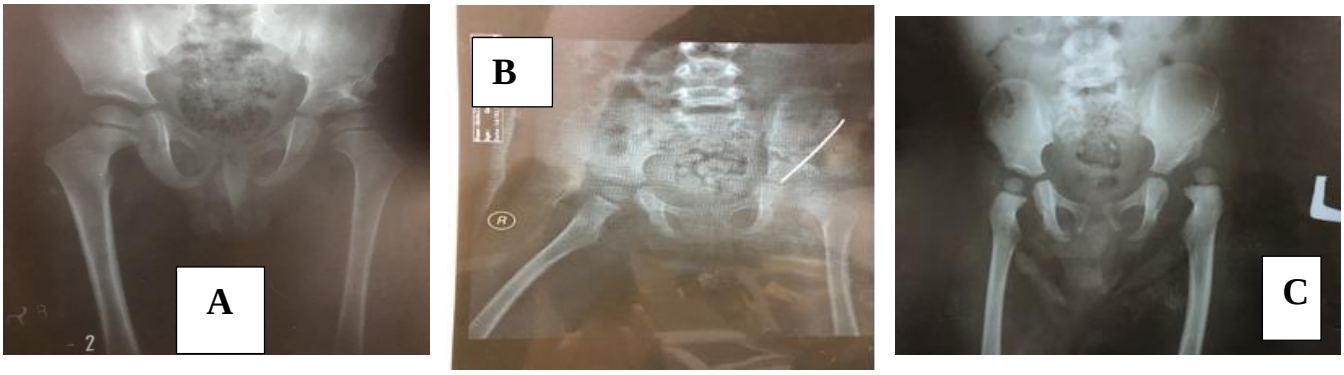

Figure 1: A 32 month old child with Lt. side DDH.
A: One- year post-operative x-ray confirmed containment, growth, and remodeling of the acetabular roof.
B: Open reduction with Salter Innominate Osteotomy postoperatively.
C: Preoperative x-ray with Lt. sided DDH.

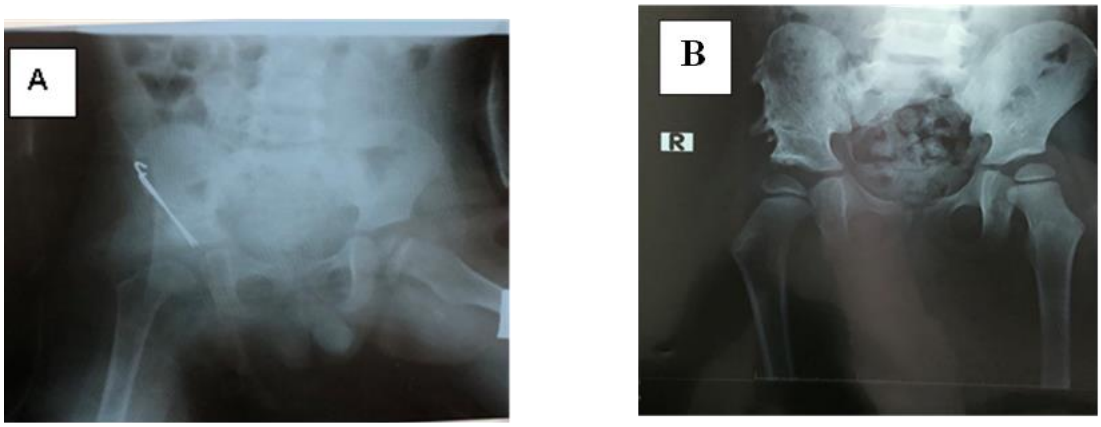

Figure 2: A 2.5 year old child with right side DDH.

A: post-operative X-ray after open reduction and Salter Osteotomy.
B: After two years view showing congruent hip joint with development and remodeling of the acetabulum and proximal femur

DISCUSSION

Containment of the femoral head will encourage and enhance development and remodeling of both the acetabulum and the proximal femur. In a younger child, positioning the femoral head into the acetabulum helps in reciprocal remodeling of the acetabulum and proximal femur, in addition to correction of dysplasia.

Salter innominate osteotomy is safe, usually gives excellent results and should be the first step to be done during open reduction in younger age groups. Innominate osteotomy (salter osteotomy of the iliac bone) was conducted in children above 18 months of age with open reduction for the treatment of DDH and this was recommended by other workers [14-17].

Maximum potential for growth, development and remodeling of the acetabulum and proximal femur was encountered up to the age of 4 years.
In 110 hips treated operatively from the age of 12 months ----- 2.5 years, there was no need for femoral shortening, in all these patients' open reduction with or without salter innominate osteotomy was sufficient provided that containment and concentric reduction was achieved with a stable, congruent hip joint.

Most orthopedic surgeons are routinely doing derotational osteotomy of proximal femur at the time of open reduction (OR) or later about 6---weeks after the first operation (open reduction), to correct the extreme degree of femoral ante-version [21-23].

In this study there was no need for surgical intervention to correct femoral ante-version and almost always corrected spontaneously.

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Conflicts of interest: There are no conflicts of interest**.**

CONCLUSION

In all children with developmental dysplasia of the hip younger than 2.5 years of age, even those cases underwent surgery including open reduction with or without salter – innominate osteotomy, there will be spontaneous correction of the extreme of femoral ante-version and there was no indication for de-rotational osteotomy of the proximal femur even in extreme degree of femoral ante-version.

This indicate that up to the age of 2.5 years, a maximum ability of self-correction, development and remodeling of the proximal femur will encounter and indicate the upper age limit for spontaneous correction of femoral ante-version to be achieved without surgery.

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Original article

Does mitomycin-C and triamcinolone injection therapy during optical urethrotomy able to reduce the recurrence of urethral stricture? A comparison study.

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Abstract:

- ***Background***: Male urethral stricture is one of the common diseases. Stricture disease may lead to severe complications which badly affect the quality of life like urinary tract infection, vesical stones, urethrocutaneous fistulas, sepsis, and finally renal impairment. Due to its high recurrence rates, it is one of the most complex and challenging issues in urological practice. The aim of the study is to evaluate the effect of intralesional mitomycin-C and triamcinolone after direct visualized internal urethrotomy on the recurrence of urethral stricture.
- ***Method and patient:*** An observational comparative study that was conducted between September 2019 and October 2021. It included 34 male participants with urethral stricture. Twelve participants were in group A in whom participants underwent direct visualized internal urethrotomy with no adjuvant treatment, 11 participants were in group B who underwent direct visualized internal urethrotomy with mitomycin-C injection and another 11 patients underwent direct visualized internal urethrotomy with triamcinolone injection were in group C. Patients were selected from outpatient clinic. Patients with idiopathic causes of stricture, traumatic non-instrumental or post-urethroplasty stricture, recurrent stricture and stricture more than 15 mm in length were excluded from the study. Follow up was done at 3, 6 and 12 months post-operatively.
- ***Result:*** In this study, only one patient among 11 who received mitomycin-C injection (9.1%) had recurrence while 2 out of 11 patients who received triamcinolone (18.2%) had recurrence. Six out of 12 patients (50%) who undergone direct visualized internal

urethrotomy only had recurrence. Adjuvant therapy decreased the recurrence rates, and the results were statistically significant. No correlation between stricture recurrence time and the type of adjuvant therapy used was found. Relationship between recurrence rate of stricture and various other variables such as age of the patient, length of stricture, stricture site and etiology were not observed in the study as the p-value was greater than 0.05.

- ***Conclusions:*** Intralesional injection of either Mitomycin-C or Triamcinolone reduces the recurrence rate of urethral strictures with statistically significant results.
- **Keywords:** Urethral stricture, mitomycin-C, triamcinolone, direct visualized internal urethrotomy.

INTRODUCTION

Urethral stricture is a known historical disease even before the century. It's peculiar to male because female urethra is wide and capacious and hardly affected by stricture disease [(1)].

Stricture disease may lead to severe complications which badly affect the quality of life like urinary tract infection, vesical stones, urethrocutaneous fistulas, sepsis, and finally renal impairment. In untreated patients, the natural history of the disease runs a severe progressive course with high rates of complications due to disease recurrence even after treatment [(2)].

Although the treatment of urethral stricture is developing, it is still one of the most complex and challenging subjects in urological work [(3)].

Urethroplasty is the gold standard and definitive treatment for urethral stricture. It is considered the most durable treatment with lifetime success rates approaching 98%. However, strictures may recur long after urethroplasty. Consequently, long-term surveillance for stricture recurrence following urethroplasty is an essential component of disease management [(4)].

The underlying etiologies of urethral stricture disease varies in different geographical areas. During the last decades, it is documented that infection-induced urethral stricture has decreased, especially in the developed countries [(5)]. The causes of urethral stricture are:

1. Iatrogenic-induced are the most common etiology for anterior urethral stricture [(3)]. Urethral catheterization is the most common iatrogenic cause, followed by hypospadias reconstruction and transurethral resection procedures.
2. Idiopathic strictures of unknown etiology occur more frequently in the bulbar urethra and are more common in younger peoples than olders (48% vs. 23%).
3. Falling astride injury causes scarring of the bulbar urethra including the surrounding spongiosum tissue.

4. Inflammatory stricture involves the infection-induced inflammatory reaction which leads to narrowing of the urethral lumen. This inflammatory stricture is considered to be the leading cause in underdeveloped countries, while in developed countries, lichen sclerosus et atrophicus is more frequently seen as an inflammatory stricture and usually involves the whole urethra [6].

Regarding the site of occurrence, the bulbar urethral strictures are the most common site (about 50%), penile urethral strictures come next (about 30%), followed by the navicular fossa (about 20%). The posterior urethral strictures are less common and frequently caused by traumatic urethral rupture secondary to pelvic bone fractures and to much less extent result from pelvic radiotherapy for treatment of prostate cancer [7].

Urethral stricture is a relatively common disease in men with an associated lifetime prevalence of 200-600 per 100,000 males. Pathologically speaking, the connective tissue of normal urethra is replaced by dense fibers interspersed with fibroblasts and a reduction in the type III to type I collagen ratio happens. These changes are accompanied by reduced ratio of smooth muscle to collagen, as well as significant loss in the synthesis of nitric oxide in stenosed urethral tissue. Spongiofibrosis of corpus spongiosum is the main pathology of anterior urethral strictures which typically happen following trauma or infection [2].

A thorough history and detailed physical examination are the key to initial diagnosis of urethral stricture. In history, we should ask about details of previous urethral catheterization or endoscopy, genital trauma, features of urethral inflammation and sexually transmitted infections such as urethral discharge, bleeding, and dysuria [8].

Obstructive and irritative voiding symptoms are the main symptoms of urethral stricture and its diagnosis should be suspected particularly in patients who have previously undergone transurethral surgery or had a history of long-term indwelling catheter during management for other disorders. Prolonged voiding time and a feeling of incomplete bladder emptying, combined with daytime and night-time frequency and urgency to void. Some patients may also be presented with typical sequelae of high voiding pressure such as prostatitis or epididymitis. Minority of patients do not present until acute urinary retention happens, since early in the course of the disease, detrusor hypertrophy can compensate for the raised bladder outlet resistance. This leads to a rise in intravesical pressure during urination and may be noticed on ultrasonography as a thickening of the bladder wall. Later, decompensation of the bladder voiding function and incomplete voiding will occur with raised post-void residual urine volume, which may progress into complete urinary retention. At the end, these changes can lead to secondary urinary tract obstruction or high-pressure vesicoureteral reflux, either of which may lead to impairment of renal function [7].

During physical examination, the clinician should examine the urethra to identify fibrotic tissue and look for skin changes (e.g., Balanitis xerotica obliterance), the presence of mental stenosis, cellulitis, fistulas, or abscesses, the presence and quality of foreskin to potentially use in later urethral reconstruction and the presence of scars from previous trauma or surgical repair. These surgical scars may reveal important information about the type of prior reconstruction which is sometimes unknown to the patient. Ideally, the examination of the patient also includes a digital rectal examination (benign prostatic hyperplasia; prostatitis) and an evaluation of the scrotum and testicles which might reveal an epididymitis or an orchitis [(9)].

Typical options for evaluation of urethral stricture include uroflowmetry, urethroscopy, retrograde urethrography (RUG), voiding cystourethrography (VCUG), and color doppler ultrasound. The AUA guidelines insisted that retrograde urethrography and/or urethroscopy are necessary to make the diagnosis of a urethral stricture [(10)].

The approach to urethral stricture disease is mainly driven by the anatomical site of the stricture, whether it is in the penile, bulbar, or posterior urethra, and its relationship to the external urethral sphincter muscles [(11)]. Dilation and direct visualized internal urethrotomy (DVIU) continue to lead the treatment for urethral strictures. The principle of DVIU is to incise the stricture by cold or hot knife or laser fiber following which, a catheter is left in situ for several days to splint the urethra open, allowing re epithelialization [(12)]. The most performed procedures for treatment of stricture diseases among board-certified urosurgeons are dilation (95%) and DVIU (85%). However, these minimally invasive procedures are characterized by a well-documented high failure rate [(13)]. The most common early complications of DVIU are urethral bleeding and perineal hematoma with up to 20% incidence of each of these complications. The most frequent late complications include erectile dysfunction, in 7% of cases, and recurrence of stricture in 50% [(14)].

Urethroplasty is the definitive surgical treatment for urethral stricture and enjoys a high success rate between 85 and 90% for simple procedures and about 80% for extremely complex repairs. Data show that when compared with urethral dilation or DVIU, open urethroplasty provides the best chance at definitive success with low recurrence rate [(13)]. In fact, multiple studies evaluated cost-effectiveness of treatment of urethral strictures and found that either early or immediate urethroplasty or a single attempt at DVIU, followed by urethroplasty if its failed. This strategy is more cost-effective than long-term dilation, or multiple DVIU procedures with urethroplasty used only as salvage procedures after failure of several attempts do dilation or DVIU [(14)].

Although numerous percentages of patients undergoing initial minimally invasive treatment of urethral stricture can achieve successful early outcome with satisfactory results, a significant percentage of patients may develop recurrent, refractory or recalcitrant stricture disease. Hence,

this group of patients with recurrent disease may pose clinical dilemmas and their definitive management can be challenging to reconstructive urosurgeons with high failure rate of salvage urethral reconstructive procedures [29]. Table 1 lists the factors which should be considered as risk factors for recurrence of urethral strictures [15].

Table 1. Factors important for urethral stricture recurrence [15].

Age	Length	Location	Etiology	Recurrent
Good prognosis	<2cm	Bulbar urethra	Idiopathic	No
Poor prognosis	>2cm	Penile urethra	Inflammatory, Iatrogenic, Lichen sclerosis	Yes

Mitomycin-C is an antibiotic with cytotoxic properties first isolated from Streptococcus caespitosus and later shown to have potent antineoplastic actions in vitro and in vivo. MMC as a potential antifibrotic agent and intravesical chemotherapeutic agent to treat urological conditions and tumors shows promise to decrease and delay the recurrence rates of many neoplasms with minimal toxic systemic side effects [16]. In a very recent data from interesting studies, their work up studied the efficacy of using intralesional MMC (injections of 0.4-mg/mL MMC in 0.2- to 0.4- mL aliquots at various points along the length of each incision for a total volume of 10 mL) with clean intermittent catheterization (CIC) and visual internal urethrotomy (VIU) for management of recurrent urethral strictures and bladder neck contractures and they finally offered all of these interventions and maneuvers can provide minimally invasive and widely available tools for managing urethral strictures which is less than 3 cm and bladder neck contractures specially for patients who are poor candidates for or refuse open surgery [17]. Side effects of systemic mitomycin include nausea, vomiting, rash, fever, bone marrow suppression, diarrhea, stomatitis and malaise. Uncommon but potentially severe adverse events include hemolysis, neurological abnormalities, hemolytic uremic syndrome, renal impairment and interstitial pneumonitis [18].

Triamcinolone falls under the class of corticosteroids—specifically a glucocorticoid. It exhibits anti-inflammatory and immunosuppressant activity via inhibiting the phospholipase A2 enzyme on the cell membrane phospholipid layer, and thereby hinders the breakdown of leukocyte lysosomal membranes and prevents the formation of arachidonic acid. It ultimately reduces the expression of cyclooxygenase (COX) and lipoxygenase (LOX) and thus prevents the biosynthesis of prostaglandins and leukotrienes, respectively [19]. Corticosteroids manifest anti-inflammatory effects via inhibiting macrophage and leukocyte migration to the affected site by reversing vascular dilation and permeability. These actions work to minimize edema, erythema, and pruritus. An important anti-inflammatory mechanism gets mediated by the inhibition of

nuclear factor kappa-B (NF-kappa-B) which leads to decrease protein expression of interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemo-attractant protein-1 (MCP-1), COX-2(20). The aim this study to evaluate the effect of intralesional mitomycin-C and triamcinolone after direct visualized internal urethrotomy on the recurrence rates of urethral stricture and timing of recurrence.

PATIENT and METHOD

This study was a comparative study which involved 34 male patients diagnosed with urethral stricture divided into three groups:

1. Group (A) with 12 participants underwent direct visualization internal urethrotomy.
2. Group (B) with 11 participants underwent direct visualization internal urethrotomy with submucosal MMC injection.
3. Group (C) with 11 participants underwent direct visualization internal urethrotomy with submucosal triamcinolone injection.

The study was conducted between September 2019 to October 2021. Participant had been selected from outpatient clinic. A questionnaire had been prepared and a detailed full urological and medical history had been obtained. All patients reported features of urinary obstruction. Full clinical examination had been conducted and laboratory investigations had been ordered for the participants and involved complete blood count and general urine examination. Diagnosis has been confirmed by both flexible cystoscopy and retrograde urethrography (RUG).

Participant should have the following criteria in order to be involved in the study:

1. Aged between 20 – 60 years.
2. First time stricture
3. Stricture due to either infection or instrumentation
4. Stricture less than 15mm in length

Any participant with any of the following settings has been excluded from the study:

1. Age less than 20 years and more than 60 years
2. Idiopathic causes of stricture
3. Traumatic non instrumental or post urethroplasty stricture
4. History of recurrent stricture
5. Stricture more than 15 mm in length

Prophylactic antibiotics in the form of third generation cephalosporin or fluoroquinolone were given to all patients 1 hour prior to surgery. For group A, direct visualization internal

urethrotomy (DVIU) was done under anesthesia using a rigid cystoscope with cold knife. Incision of the stricture was done at 12 o' clock along the stricture length. Foley catheter has been placed for all patients and had been removed after 5-7 days plus prophylactic antibiotic were prescribed. Mitomycin-C and triamcinolone were prepared at the day of operation. MMC vial 10 mg were diluted with 100 cc normal saline.

In group B, following direct visualization internal urethrotomy, 1 ml of 0.1 mg/ml of mitomycin-C was injected at the edge of the scar at multiple sites for every 1 cm of stricture using metallic needle used for Botox injection or INJETAC needle. Foley catheter has been placed for all patients and had been removed after 5-7 days plus prophylactic antibiotic were prescribed. In group C, following direct visualization internal urethrotomy, 1 ml of 40 mg/ml of triamcinolone suspension was injected at the edge of the scar at multiple sites for every 1 cm of stricture using metallic needle used for Botox injection or INJETAC needle. Foley catheter has been placed for all patients and had been removed after 5-7 days plus prophylactic antibiotic were prescribed. All participants were being followed up initially after the surgery to look for complications. Late follow up was done at 3, 6- and 12-months post operatively. Inquiries about urinary tract obstruction features with clinical examination were obtained. Urethroscopy and retrograde urethrography was performed at each visit.

The statistical analysis of the data was done, and quantitative continuous variables were presented as mean and standard deviation. Categorical nominal and ordinal variables were presented in the form of frequencies and percentages. One-way ANOVA test was used to compare the continuous variables among study groups accordingly. To test for normal distribution, a Z test were used. Chi square test had been conducted to compare the categorial variables. Kruskal–Wallis test were conducted to compare quantitative with nominal data out of normal distribution. A level of P-value less than 0.05 was considered significant. All patients were informed about methodology and purpose of study and written consent was obtained.

RESULTS

The age of participants was ranging from 21 to 60 years with a mean of 40.0 years ± 12.136 standard deviation with different age range among different causes of urethral stricture. In terms of stricture site, most of the participants had stricture at bulbar urethra with a percent of 66.7%, 72.7% and 63.6% for group A, B and C respectively. The percent of patients with stricture at the penile urethra were 33.3%, 27.3% and 36.4% for group A, B and C respectively. The stricture was due to either an infection or trauma due to instrumentation but most of the patients had a secondary stricture due to infection with a percent of 66.7%, 63.6% and 54.5 % for group A, B and C respectively. The rest of patients were due to instrumentation.

Only one patient from 11 in group B (MMC) had recurrence with a rate of 9.1% while in group C (triamcinolone), 18.2% (2 patients) of the participant had a recurrence. In the control group A, 50% of participant had recurrent urethral stricture. it is clear that the result is statistically significant for those who had MMC and triamcinolone injection as the p-value is 0.027.

Table 2. Recurrence rates among different study groups.

	Group A		Group B (MMC)		Group C (Triamcinolone)	
	Number	Percent %	Number	Percent %	Number	Percent %
Recurrence	6	50.0	1	9.1	2	18.2
No recurrence	6	50.0	10	90.9	9	81.8

Although the stricture recurrence time mean in patients received MMC were longer than the other groups, correlation between recurrence time and type of adjuvant therapy is not significant as the Kruskal-Wallis H value was about 0.858 and the p-value was 0.651. This correlation is illustrated in table3.

Table 3. Average stricture recurrence time among study groups.

	Group A	Group B (MMC)	Group C (Triamcinolone)	P value
	Mean ± STD	Mean ± STD	Mean ± STD	
Recurrence time (months)	7.17 ± 3.971	11.0 ± 0	9.5 ± 3.536	0.651

The mean of stricture length in participants who had recurrent urethral stricture is 9.67+2.875, 14.0+0, 11.0+828 for group A, B, and C respectively. When conducting statistical analysis to correlate between these variables, it appeared that there is no statistical correlation as the p-value is 0.521. The mean of age in participants who had recurrent urethral stricture is 47.0 ± 8.319, 32.0 ±0, 44.0 ± 12.728 for groups A, B, and C respectively, which seems to be statistically insignificant as the p-value is 0.643.

Regarding etiology of stricture and stricture recurrence, 6 patients with post infectious stricture had recurrence: 3 of them in group A, 1 in group B (MMC) and 1 in group C (triamcinolone). Three patients with post-instrumentation stricture had recurrence: 2 patients in group A while only 1 in group C (triamcinolone). When comparing those data among the three study groups, we found out the stricture recurrence and etiology had no significant association as the p-value was 0.724, as seen in figure 1.

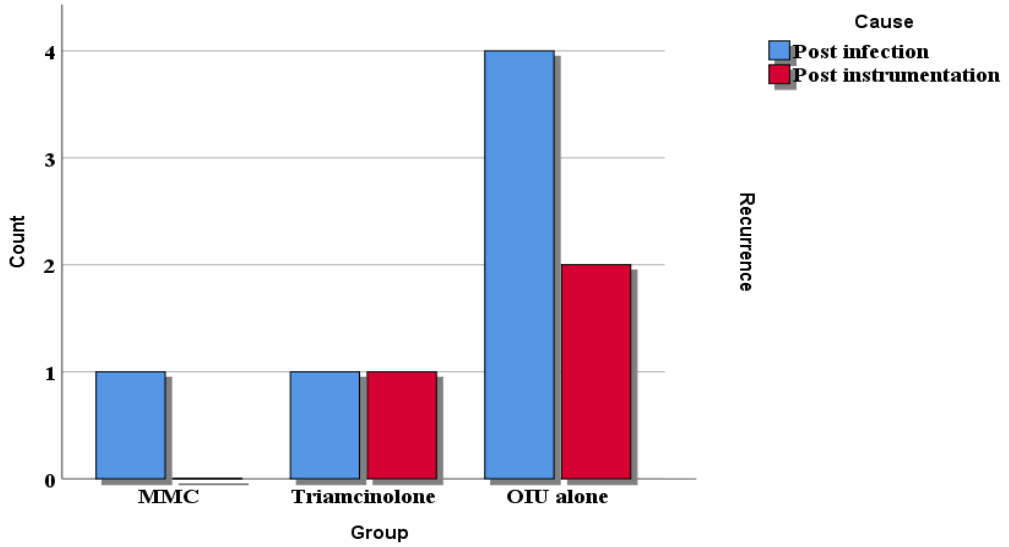

Figure 1. Stricture recurrence and etiology.

It is shown that the stricture recurrence in regard to stricture site, 7 cases of bulbar stricture had recurrence; 5 cases in group A while 2 cases in group C. Two cases of penile stricture had recurred; one case in group A and the other case in group B. Again, no statistical correlation was found between the site and stricture recurrence as the p-value was 0.449, as shown in figure 2.

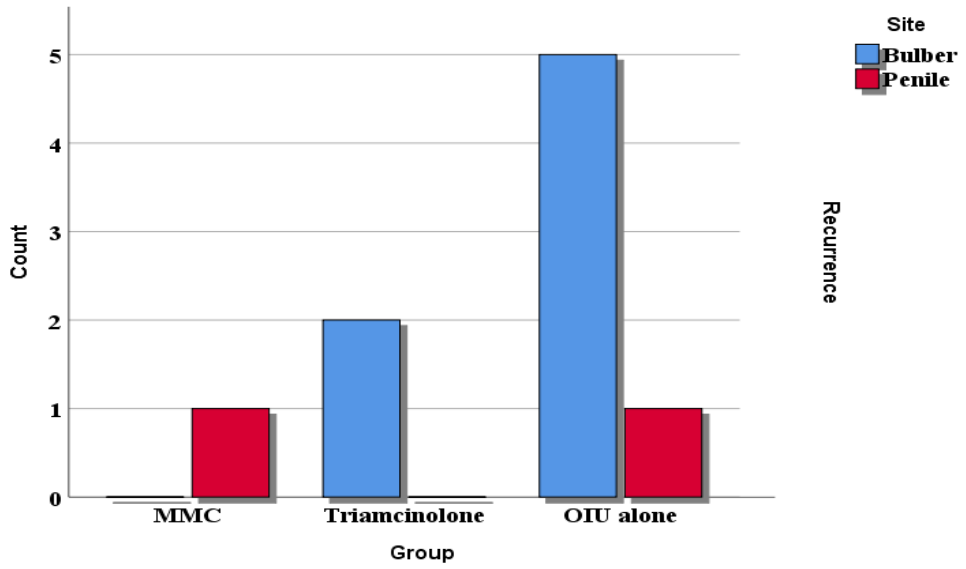

Figure 2. Stricture recurrence and site of stricture.

DISCUSSION

When comparing our data with patients did direct visualization internal urethrotomy without adjuvant treatment (50% had recurrence); the data was statistically significant as the p-value was 0.007 (group B); this agrees with Ali et al [21] and Farrell et al [22]. Ali et al found that 14.1% of participants with DVIU and MMC injection had recurrence as compared to 36.9% rate of recurrence for those undergone DVIU alone. Farrel et al found that 75.7% of participants had no recurrence with DVIU and MMC injection. For those who underwent DVIU and triamcinolone injection, our study conducted that the recurrence rate was 18.2% with a statistically significant p-value of 0.035 which agrees with Mazdak et al [23] and Yıldırım et al [24]. Mazdak et al found that 21.7% of participants had recurrence for those undergone DVIU with triamcinolone injection while 50% for those who undergone DVIU alone had recurrence [23]. Yildirim et al found that a lower rate of recurrence with triamcinolone injection (5% of participants) [24].

After following up the patients for 12 months, our study showed that it took those patients after MMC injection longer time to recur but statistically; no correlation between stricture recurrence time and the type of adjuvant therapy used was found as the p-value was 0.651. This result disagrees with Ali et al as it states that most of participants with MMC injection had recurrence at mean of 6 months following injection which was more delayed than those undergone DVIU alone and it was statistically significant [21]. This difference could be possibly explained previously by the larger sample size, longer follow up time and inclusion of anterior strictures

only in their study. Regarding stricture length, mean stricture length was 9.12mm but no significant correlation was found between recurrence rates and stricture length as the p-value was 0.521. This disagrees with Mazdak et al as it stated that the success rates were higher in those with shorter stricture length [23].

In terms of age, our study did not find a correlation between age of the participants and stricture length as the p-value was 0.643. Regarding etiology of stricture, despite the slightly higher success rates in post instrumentation cases, those results were not significant statistically with a p-value of 0.724. Mazdak et al concluded similar results with a difference of including idiopathic cases of stricture in addition to infectious and traumatic causes in their study [23].

Regarding location, patients who had recurrence in group A involved both bulbar and penile stricture. Recurrent stricture in group B occurred in one patient with bulbar stricture while those who had recurrence in group C had penile location of stricture. Overall, no significant correlation was recorded between stricture site and recurrence with a p-value of 0.449.

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Conflicts of interest:

There are no conflicts of interest**.**

CONCLUSION

Supplemental injection therapy of urethral stricture during urethrotomy incision procedure confirmed better recurrence rate than stricture incision alone, but larger sample studies with longer follow up periods are required to better outline the benefit of theses adjuvant drugs, and their dosage and drawbacks.

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Original article

A Double Cerclage and Tension band Wiring Technique Fixation for Comminuted Patellar Fractures

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Abstract:

- ***Background***: When the patella is fractured it should be repaired and patellectomy should be avoided as much as possible even in comminuted fractures. In comminuted patellar fractures, a combination of cerclage wiring and tension band fixation is confirmed to provide good mechanical stability. The objective of the present work was to find out the effectiveness of comminuted patellar fracture fixation with combined cerclage and tension band wiring technique.
- ***Method and patient:*** Forty- six patients underwent surgical stabilization for comminuted patellar fracture between year 1996 to 2016. All fractures were classified as 34-C3 according to the Orthopedic Trauma Association Classification. All the patients were underwent open reduction- internal fixation with combined Cerclage and tension band wiring technique.
- ***Result:*** Fracture healing was occurred within an average of 3- 5 months, while in bilateral cases it was 4 - 8 months. Full range of knee movements was seen in 42 (91.3 %) cases and knee flexion more than 120º was seen in 4 (8.7 %) cases. Quadriceps power was normal in 44 (95.6 %) cases, but 2 cases had quadriceps power of grade-IV. No extensor lag and no quadriceps atrophy were seen in any cases. Forty four (95.6 %) patients could squat fully and two (4.3 %) patients could squat up to half of the normal level. All patients were able to climb up and down stairs without any problem.
- Most patients have no subjective complaints like pain, difficulty in walking, difficulty in squatting and climbing. The clinical results after operation were evaluated by the clinical

grading scales of Böstman including range of movement, pain, work, atrophy, assistance in walking, effusion, giving way, and stair-climbing during follow-up. There were no significant complications, such as infection, knee stiffness, and non-union or implant failure in any of the cases. The average follow-up period was 8 months (Ranged 6 – 18 months).

- ***Conclusions:*** This study had concluded that combined Cerclage and tension band wiring technique was a successful surgical treatment for comminuted fractures of the Patella.
- **Keywords:** Comminuted patella fracture, cerclage wiring, tension band wiring.

INTRODUCTION

Fractures of the patella are common and constitute almost 1% of all skeletal injuries, present a higher prevalence within the age group of 20 to 50 years old. Comminuted patellar fractures are often caused by high – energy trauma, occur in young individuals [1-8].

Twice the force is required to extend the last 15º of extension of the knee than to extend from fully flexed position to 15º short of full extension [9].

The knee requires something that increases the moment arm during extension so that it can maintain a constant level of torque. Patella provides this mechanical advantage [2-7].

Kaufer in 1971, on the basis of experimental work showed that the patella was not without importance in the knee joint and was responsible for improving its efficiency and 30% increase in the pull of quadriceps is necessary to compensate for the loss of patella [10-17].

The patella is an important component of the extensor mechanism of the knee, significant disability and decrease in knee extension power and function is seen following patellectomy [8-22].

Marya et al. studied the outcomes of patellar fractures submitted to osteosynthesis and patellectomy and found 80% of excellent outcomes in the first group and 50% in the second. Therefore, when the patella is fractured it should be repaired and excision of the patella should be avoided as much as possible even in comminuted fractures [20-22].

At present, the treatment methods of patellar comminuted fracture include the following: Circumferential cerclage wire fixation, modified tension band fixation, nickel-titanium patella concentrator, titanium cable cerclage and Partial or total patellectomy [23–24]. Partial or total patellectomy results in the destruction of the extensor mechanism and normal patellofemoral joint contact surface, which reduces knee joint function, accordingly, open reduction and internal fixation is the first choice for the treatment of comminuted patellar fracture [2-13,24-27].

Circumferential cerclage wire fixation is suitable for the treatment of a comminuted patellar fracture. Some scholars reported that two or more fixation methods were combined to treat patellar comminuted fracture, such as circumferential cerclage wire fixation combined with modified tension band [28-31]. There is no universally accepted treatment for comminuted patellar fractures. The Orthopedic Trauma Association classification (OTA) by Muller (1979) is still the most useful comprehensive classification system for describing fractures of the patella [25-27]. Bostrom (1972) accepted 3-4 mm fragment displacement and 2-3 mm articular incongruity for non-operative treatment. While surgical stabilization was usually indicated If fragments are displaced more than 3-4 mm if articular incongruity more than 2–3 mm present and osteochondral fracture with displacement of fragment in the joint [3]. The objective of this study was to describe the result of surgery for 46 patients with comminuted patellar fractures treated by the technique of cerclage loop wire fixation and standard tension band principle, both applied together without using kirschner wires.

PATIENT and METHOD

The work was conducted at two different teaching hospitals in Kirkuk and Erbil city between year 1996 to 2016. Forty- six patients underwent surgical stabilization for comminuted patellar fracture, with a average age of 34 years (range, 20 – 62 years) , unilateral patellar fracture occurred in 44 patients and was bilateral in 2 patients , male patients were affected in 34 patients (74 %) and only 12 patients (26 %) were female .

The cause of the injury was road traffic accident in 38 patients and fall on knee in 8 cases (fall from a height). All fractures were classified as 34-C3 (based on Orthopedic Trauma Association classification).

Interval between trauma and surgery was less than 48 hours in 40 cases and more than 10 days in 2 cases. Four cases were open fracture - type 1- requiring urgent wound debridement, irrigation and osteosynthesis of the patella.

Surgical procedure

The operation was performed under general or spinal anesthesia.

Tourniquet was applied to the upper part of the thigh and the part was painted with iodine and spirit and draped.

A longitudinal midline skin incision was made over the patella, the skin and fascia were retracted to expose the fracture site.

The knee was flexed to 15 – 20 degrees, the extensor apparatus was exposed, the patellar fracture fragments, medial & lateral parts of the retinaculum and the patellar tendon should be

exposed and to observe the pattern of fracture fragments displacement and to assess the extent of damage to extensor expansions around the patella. The quadriceps apparatus tear was seen in all cases. Anatomical reduction & alignment of the fracture fragments should be obtained, with great attention should be directed toward perfect reduction of the posterior articular surface of the patella.

Surgical technique – wiring

The operative procedure performed by using the technique of double wire fixation (both wires were of 18 G braided stainless steel) applied in two planes, at first both wires should be passed deep to the insertion of the quadriceps tendon above the patella and beneath the patellar ligament below the inferior pole of the patella.

The first cerclage wire applied circumferentially in the deep plane at the periphery of the posterior articular surface of the patella like cerclage loop wire application (figure of 0) and the second wire should cross over the anterior surface of the patella in tension band principle (figure of 8) – configuration.

The operative time was short ranging from 30 to 40 minutes.

The stability and efficiency of the fixation and the maintenance of reduction of the fragments must be tested by forcing the knee to be flexed up to 90 degrees (s. t into full flexion) and into full extension, by repeating this movements once or twice, the surgeon must be sure under direct observation that the anatomical alignment of the fragments at the posterior articular surface will remain in perfect reduction and there will be no any separation or displacement will occur . Repair of medial and lateral retinacular tears was mandatory to strengthen the extensor expansions at medial, lateral sides and over the anterior surface of the patella. Repair of retinacular attachments around the patella was found to add more stability in addition to the major stability achieved from union after bony healing at the patellar fracture lines.

In these patients' patellectomy was not indicated even in severely comminuted fractures because anatomical reduction, stable fixation, repair and reconstruction was possible for the anterior knee structures including quadriceps expansions, retinacular repair, patellar fracture fragments and patellar ligament.

The affected knees were protected with a cylinder back slab for 2 weeks. The patient was advised to start quadriceps exercises from the first post operative day. Flexion of the knee joint to 90 degrees should be encouraged after 2 weeks postoperatively.

Partial weight bearing was started 4 – 6 weeks after the surgery. Full weight bearing was allowed in all cases 8 weeks after the surgery.

RESULTS

Forty six patients with comminuted fracture patella were included in this study. Majority of cases (32 patients) about 70% were in the age group of 25 – 40 years. The youngest patient was of 20 years age and oldest was 62 years of age. Fracture healing was occurred within average of 3 - 5 months, while in bilateral cases 4 - 8 months, fracture union was confirmed on follow – up x – rays when the fracture lines was not visible, trabecuale were seen across the fracture sites and no bony absorption occurred at the fracture lines. The average follow-up period was 8 months (range, 6 – 18 months).

Each follow up patients were questioned about subjective complaints like pain, difficulty in walking, squatting, climbing, and stepping downstairs and the ability to perform normal daily activity. The full function of the knee joint should correspond to the achievement of around 140 degree of knee flexion. By end of the fourth postoperative month.

Range of movements of knee seen full in 42 cases (91.3 %) and knee flexion more than 120º in 4 cases (8.7 %). Quadriceps power was normal in 44 cases (95.6 %) but 2 cases (4.3 %) had quadriceps power of grade-IV. No extensor lag and No quadriceps atrophy were seen in all cases.

All patients were able to climb up and down stairs without any problem.

Most patients suffered from discomfort and irritation of the skin by the implant - wire. Bursa was seen in two patients. Most patients have no subjective complaints like pain, difficulty in walking, difficulty in squatting and climbing.

Early mobilization provided good outcomes, because it allows for a wider ROM. Late mobilization undoubtedly determined a stronger joint stiffness.

There were no significant complications, such as infection, Knee stiffness, non-union or implant failure in any of the cases. The cases were graded according to Böstman clinical scale assessment: Forty patients (87 %) were graded excellent and good results in six patients (13%).

Table 1: Demographic and preoperative clinical characteristics of the patients

Clinical characteristics	Frequency	Percentage (%)
Gender		
Male	**34**	**(73.9)**
Female	**12**	**(26.1)**
Site of the fracture		
Unilateral	**44**	**(95.7)**
Bilateral	**2**	**(4.3)**
Cause of the injury		
Car accident	**38**	**(82.6)**
Fall on the knee	**8**	**(17.4)**
Fracture classification		
34-C3.1	**0**	**(0.0)**
34-C3.2	**46**	**(100.0)**
Total	**46**	**(100.0)**

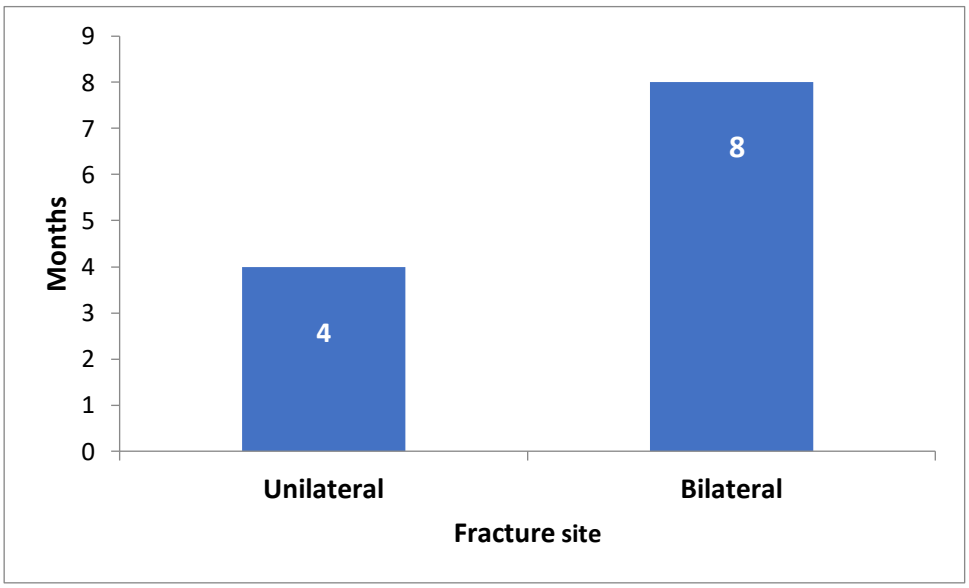

Figure 1: Mean fracture healing of the patients in months

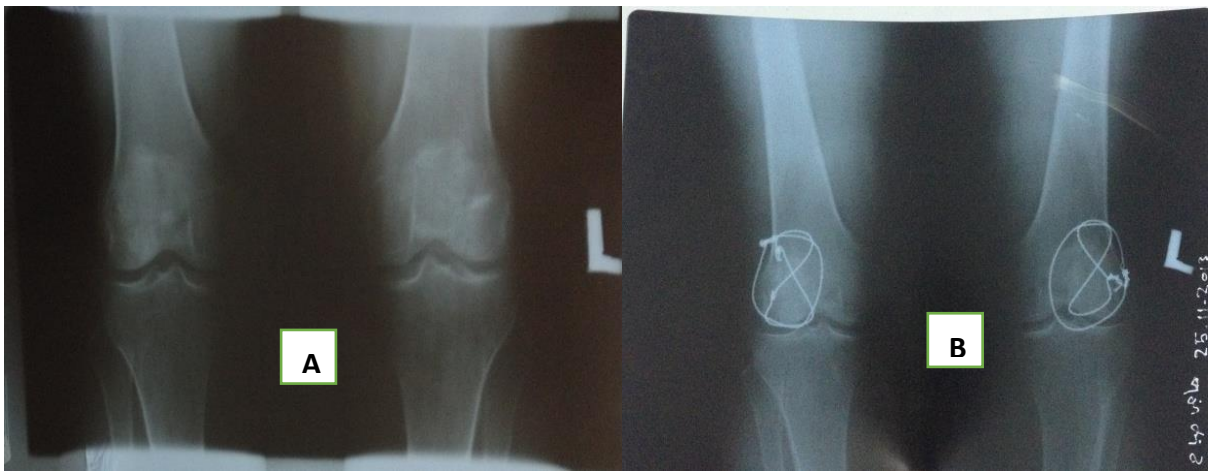

Figure 2: A 58 year old patient with severe comminuted bilateral patellar fracture.

A: After removal of the wires bilaterally - with healing of the fracture

B: Bilateral fixation for comminuted fracture patella - post-operative x – ray

Table 2: Postoperative clinical characteristics of the patients

Clinical characteristics	Frequency	Percentage (%)
Knee movement		
Full range	**42**	**(91.3)**
More than 120º	**4**	**(8.7)**
Quadriceps power		
Normal	**44**	**(95.7)**
Grade IV	**2**	**(4.3)**
Squatting position		
Full squatting	**44**	**(95.7)**
Half squatting	**2**	**(4.3)**
Treatment outcome		
Excellent	**40**	**(87.0)**
Good	**6**	**(13.0)**
Total	**46**	**(100.0)**

DISCUSSION

Clinically the aim of surgery was to achieve fracture healing, to restore normal quadriceps power and full range of knee movements, to avoid joint incongruity at the posterior articular surface of the patella to prevent post-traumatic arthritis at patello-femoral joint.

As early as in 1909, Heineck reviewed 1100 patella fractures and concluded that total patellectomy for simple fractures is to be condemned. He recommended that patellectomy should be done only in severely comminuted fractured [6,13-15].

Campbell observed that total patellectomy has a role only in severely comminuted and grade-III compound fractures [1,2].

In this study the result of surgery on 46 patients with comminuted patellar fractures was assessed and, in most patients, it was found that the activity of daily living Scale (ADLS - score) of the Knee was good and full range of knee motion (ROM) was achieved by end of the fourth postoperative month. Excellent outcomes were found in (87 %) of the cases, and good outcomes were seen in (13 %) of patients. These findings were comparable to Dudani and Sancheti (1981) [22], and comparable with that of Srinivaslu et al. (1984) [2,3].

This procedure was found to be an effective surgical intervention for the treatment of comminuted patellar fractures because complete healing of the fracture and full range of knee motion (ROM) was achieved in nearly all cases.

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Conflicts of interest: There are no conflicts of interest**.**

CONCLUSION

The patella is essential for effective function of quadriceps and for proper biomechanics of knee joint so it should be preserved wherever possible.

A combination of cerclage wiring and tension band fixation was found to be a successful surgical technique for treatment of comminuted patellar fractures.

Normal functioning knee joint is very important especially in a country like Iraq where social habits and needs require a full range of knee flexion. Most of our patients were satisfied with range of motion gained particularly necessary for the oriental habits of squatting and sitting cross-legged.

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Original article

ULTRASOUND MEASUREMENT OF OPTIC NERVE SHEATH DIAMETER IN A SAMPLE OF IRAQI ADULTS

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Abstract:

- ***Background***: Intracranial hypertension is a common life and vision threatening condition, intracranial pressure (ICP) can only be measured by invasive procedures. Distension of optic nerve sheath in association with raised ICP has been proven by the clinical trials. Transorbital sonographic measurement of optic nerve sheath diameter (ONSD) can be a simple noninvasive method for detection of raised ICP, however until now there is no consensus on upper normal limit of ONSD. The aim of the study is to measure optic nerve sheath diameter (ONSD) in healthy adults to provide normative data in a sample of Iraqi population.
- ***Method and patient:*** an observational cross-sectional study was conducted in Ibn Alhaitham eye teaching hospital, Baghdad, Iraq. Both eyes of 98 healthy adult volunteers aged 19 to 77 were examined using Absulu ultrasound machine with 20 MHz annular probe. Two measurements of ONSD were taken 3mm behind the eye globe and the average was calculated.
- ***Result:*** Optic nerve sheath diameter measurements ranged from 3.78mm to 7. 13mm.The mean was 5.54mm with standard deviation of 0.59mm and a median of 5.56mm. The 95% percentile was 6.53mm. There was no statistically significant relationship between ONSD measurement and gender or age.
- ***Conclusions:*** The mean ONSD measured by transorbital ultrasound was 5.54mm and the upper normal limit was 6.5mm (95% percentile) in a sample of Iraqi population.

- **Keywords:** Intracranial hypertension, intracranial pressure, optic nerve sheath, transorbital ultrasound.

INTRODUCTION

Intracranial hypertension is a common life and vision threatening syndrome caused by a variety of neurological and non-neurological diseases. Invasive intracranial devices that are either intra-parenchymal or intra-ventricular remain the gold standard for intracranial pressure (ICP) measurement. However, this technique is invasive and not always feasible due to a lack of facilities or contraindications such as coagulopathy. Moreover, ICP monitors can lead to complications such as hemorrhage, malfunction, or infection [(1)].

Neuroimaging by computed tomography (CT) scan and magnetic resonance imaging (MRI) can be used to predict intracranial hypertension, but these techniques are expensive, need long acquisition times, have limited availability, and impose harmful radiation exposure. Furthermore, CT scan has poor performance for detection of raised ICP [(2)].

Lumbar puncture opening pressure can also be used to diagnose elevated ICP. However, lumbar punctures carry risks as well, such as infection or bleeding, and can be time and resource intensive if performed on a critically ill patient [(3)].

Any pressure rises within the intracranial compartment impacts on the optic nerve head as swelling of the optic disc (papilledema). Ophthalmoscope examination for papilledema is one of the means for detecting raised ICP but the development of papilledema can take hours to many days [(4)], besides requiring a skilled observer for precise identification and differentiation from pseudo-papilledema which is not always possible.

Dilatation of the optic nerve sheath has been shown to be a much earlier manifestation of ICP rise [(5)]. Direct communication has been documented between the subarachnoid space of the optic nerve and the chiasmal cistern of the brain [(6)]. This communication allows the free transfer of CSF between the two compartments and possibly explains the intrathecal enhancement of the perioptic nerve space during myelography or cisternography [(7)]. The optic nerve sheath features a baseline diameter that remains constant as long as ICP is maintained within normcisternography. (ICP rises, CSF flows towards the perineural subarachnoid space and increases the pressure around the optic nerve. This results in expansion of the dural sheath and an increase in the ONSD [(8)]. Liu et al [(9)] confirmed the above phenomenon in fresh cadavers by performing saline infusions through a ventriculostomy to achieve various levels of ICP. They observed a linear relationship between the ICP, and the subarachnoid pressure of the optic nerve as recorded through an orbitotomy. Using optic nerve sonography or magnetic resonance imaging, several studies have demonstrated enlarged optic nerve sheaths in children and adults with raised ICP due to various pathologies and have established that increased ONSD is a sensitive sign of intracranial hypertension [(10)]. There is also evidence that enlargement of the

optic nerve sheath is not a static indicator of intracranial hypertension but a dynamic phenomenon which varies with changes in the ICP [8].

Direct visualization of the optic nerve is possible by means of sonography. The method was pioneered in the 1970s by Ossoinig [5] who used A-scan technique to discern the optic nerve from the perineural sheath. In the next decades the B-scan technique was introduced, and the method was standardized and implemented mostly in ophthalmology for the assessment of ocular disorders. Modern high frequency transducers enable adequate penetration of the post bulbar area and quantification of the ONSD with a spatial resolution of 0.4 mm. Optic nerve sonography is relatively easy to perform and features a low inter- and intra-observer variability which is close to the intrinsic imaging ability of most modern ultrasound equipment [11]. Ultrasonographic measurement of the optic nerve sheath diameter (ONSD) a fixed distance from the retina provides a non-invasive, quick, inexpensive bedside method to predict and assist in the diagnosis of intracranial hypertension [12]. However, there has been no consensus on the optimal cut-off value of abnormal ONSD to indicate elevated ICP [13]. A wide variation is reported when ONSD was compared with invasive ICP monitoring, ranging from 4.8 to 5.9 mm [14].

The normal range of ONSD in healthy population is indispensable information to interpret the measurement of ONSD as a marker of intracranial hypertension. Moreover, it is still unknown whether there is a difference of ONSD values between Iraqi and other populations, as ONSD in Iraqi population has never been measured.

PATIENT and METHOD

A cross-sectional observational study, conducted at Ibn-AL Haitham eye teaching hospital, Baghdad, Iraq. Approval of the Iraqi board of medical specialties was obtained for the protocol of this study. A verbal consent was taken from all participants to be included in our study. Data collection started on October 2020 and ended in April 2021. No financial interests are involved in this study.

Exclusion criteria were history of any neurological disease, history of head trauma or surgery, patients taking medications that affect intracranial pressure, (mainly Vitamin A, tetracyclins, corticosteroids, oral contraceptives, cyclosporine, recombinant growth hormone and lithium), best corrected visual acuity less than 6/6 and signs of optic neuropathy on ophthalmological examination (afferent pupillary defect, optic disc swelling, pallor, and cupping).

Healthy Iraqi adults above the age of 18 years were evaluated by history taking to exclude any systemic or ocular condition that may affect intracranial pressure or the optic nerve. Ophthalmological examination included pupillary examination and visual acuity assessment by

Snellen's chart and fundus examination using slit lamp with a condensing lens (Volk 90D, Volk optical Inc. USA) to exclude signs of optic neuropathy (optic disc swelling, pallor and cupping).

Measurement of optic nerve sheath diameter was done by ultrasound B-mode examination. We used a high frequency 20 MHz ultrasound transducer annular probe from Absulu ultrasound machine, Quantel medical Inc. France done by single trained sonographer, all participants were examined in sitting position and asked to look straight forward, there is evidence that ONSD is not affected by patient position.[15] After application of coupling gel over closed eyelid, the probe is placed without pressure on the lateral half of upper eyelid with the transducer plane indicator in horizontal position, the probe is directed slightly caudally and nasally. We selected the orbit scan option provided in our ultrasound machine software. With the globe being in primary position a transverse (axial) section is taken through the globe and optic nerve complex.

The optic nerve appears as a hypoechoic band extending behind the globe surrounded by the hyperechoic orbital fat. The optic nerve sheath is identified as two dark more hypoechoic lines surrounding the optic nerve in the center. Optic nerve sheath diameter is measured 3mm behind the eye globe perpendicular to the axis of the optic nerve complex between the inner borders of the hypoechoic lines of optic nerve sheath. Two measurements were taken for each eye and the mean is calculated (figure 1). Despite the presence of an interocular symmetry between the ONSD of fellow eyes, dilatation of optic nerve sheath diameter can be asymmetrical, and cases of unilateral papilledema have been reported [16], therefore, in this study we took ONSD in each eye as a separate measurement, and in clinical practice the sonographic measurement of the ONSD should be performed bilaterally [8].

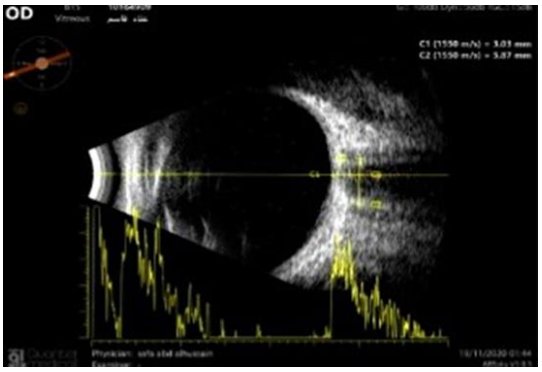

Figure 1: B- scan image showing horizontal (axial) section of optic nerve complex. hypoechoic lines of optic nerve sheath. caliber lines show our measurements taken 3mm behind the globe.

Statistical analysis of data was performed using IBM© SPSS (statistical package for social sciences software) version 26. Normality of data is tested by Shapiro-Wilk test. Mann-Whitney U test is used to compare optic nerve sheath diameter measurements between males and females. Wilcoxon matched pairs signed ranks test is used to compare measurements between right and left eyes. Kendall's-tau test is used to determine the correlation between ONSD and age. A two tailed P-value ≤ 0.05 is considered statistically significant.

RESULTS

Both eyes of 98 healthy adults are examined in Ibn-Al Haitham eye teaching hospital in an observational cross sectional study, a total of 196 eyes.

Demographic data

The age of studied sample individuals ranged between 19 and 77 years, with a mean age of 45.32 years, standard deviation 14.5 and a median of 47.5 years. Our study sample included both genders, 47 (48%) females and 51(52%) males. (Figure 2).

All volunteers were from Iraqi nationality.

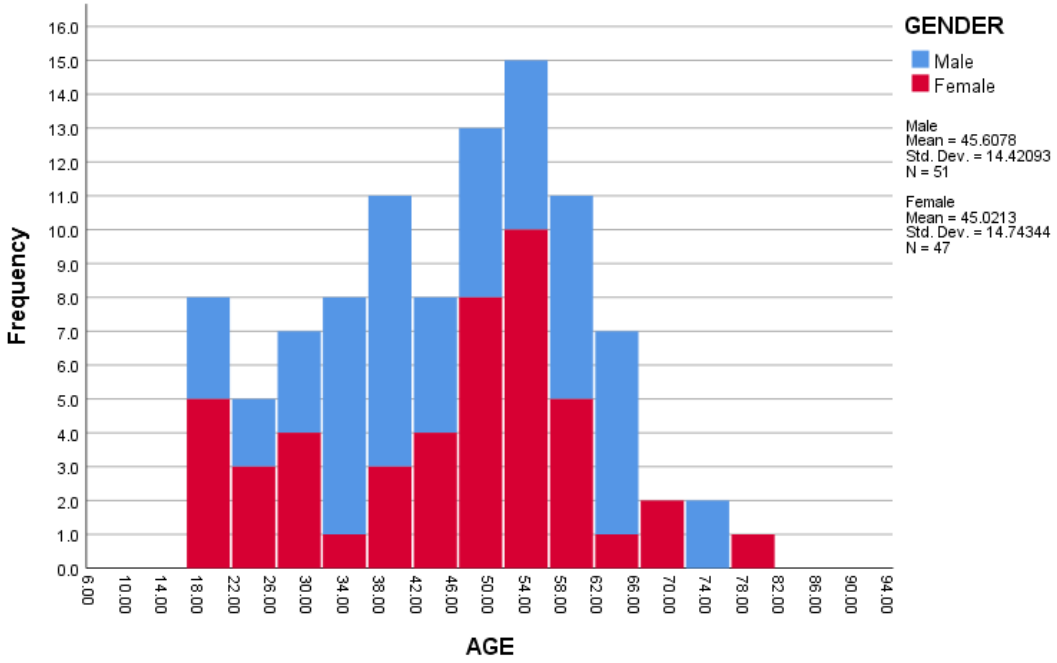

Figure 2: age and gender distribution of study sample

ONSD measurements

Intra-observer variability

Repeated measurements for the same eye by the same examiner are tested first for intra-observer variability. The intraclass correlation coefficient (ICC) was 0.82, which indicate good test repeatability. The standard error of measurement (SEM) was 0.25mm.

There was no significant statistic difference between repeated measurements of ONSD. Table 1 shows data and statistical analysis used to indicate the difference between repeated measurements.

Table 1: repeated measurements of ONSD

Side	ONSD mean ± SD		P–value*	ICC**	SEM
	1st reading	2nd reading			
Right	5.548 ± 0.62	5.542 ± 0.64	0.84	0.839	0.24 mm
Left	5.552 ± 0.62	5.524 ± 0.58	0.32	0.801	0.25 mm

*** Friedman's two way ANOVA test**
**** Intraclass Correlation Coefficient test**

Optic nerve sheath diameter

Optic nerve sheath diameter measurements in examined eyes (196) ranged from 3.78mm to 7. 13mm.The mean was 5.54mm with standard deviation of 0.59mm and a median of 5.56mm. The 95% confidence interval was 5.46-5.62mm. the 95% percentile was 6.53mm. Measured data of ONSD did not follow strict normal distribution (figure 3).

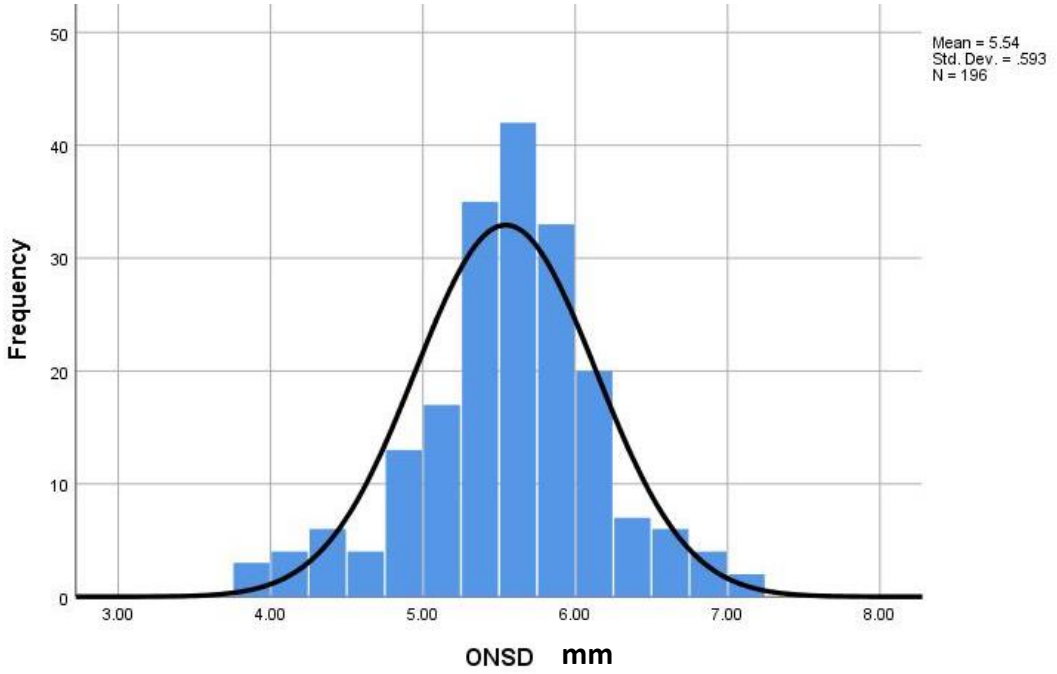

Figure 3: Mean values of ONSD histogram with normality curve

ONSD in right and left eyes

The median of ONSD in the right eye was 5.57mm. The mean was 5.54mm with standard deviation of 0.61mm. While in the left eye the median ONSD was 5.56mm, the mean was 5.53mm with a standard deviation of 0.57mm. There was no statistically significant difference in mean ONSD measurements between right and left eyes (table 2 and figure 4).

Table 2 ONSD in right and left eyes

ONSD mm	Right	Left
Mean	5.54	5.53
Median	5.57	5.56
Std. Deviation	0.61	0.57
Minimum	3.79	3.78
Maximum	7.13	7.01
P value*	0.915	
*Wilcoxon Signed Ranks Test		

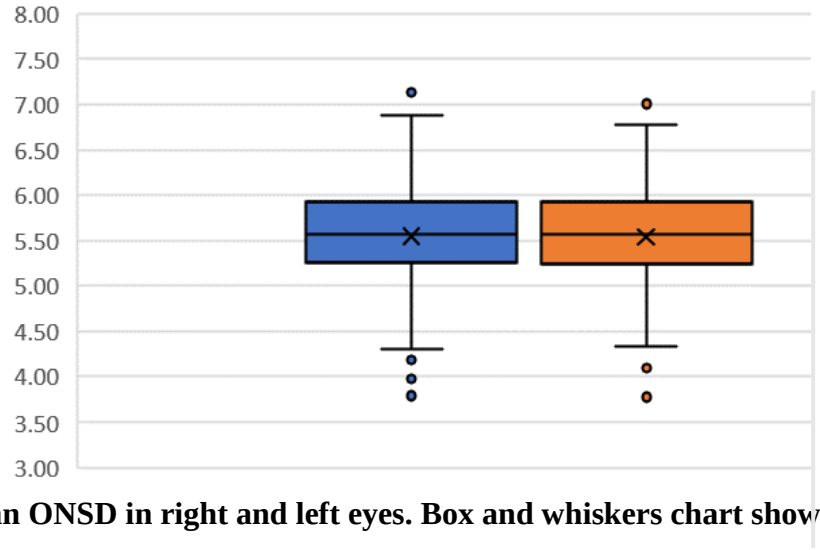

Figure 4: Mean ONSD in right and left eyes. Box and whiskers chart showing the mean (×), median (center line), quartiles (box), minimum and maximum measurements (fences and outliers)

ONSD measurements in different genders

The mean optic nerve sheath diameter measurement in males was slightly higher than females with a mean ONSD of 5.63mm, standard deviation 0.47mm, median 5.59mm and a 95% percentile of 6.60mm. While in females the mean ONSD was 5.44mm, the standard deviation 0.69mm, the median 5.50mm and the 95% percentile was 6.52mm. This difference between genders in our study was not statistically significant as the p-value is higher than 0.05 as illustrated in table 3 and figure 5.

Table 3 ONSD measurements in different genders

ONSD mm	Male	Female
Mean	5.63	5.44
Median	5.59	5.50
Std. Deviation	0.47	0.69
Minimum	4.35	3.78
Maximum	6.80	7.13
95% percentile	6.60	6.52
Number	51	47
P value*	0.076	
* Mann-Whitney U test		

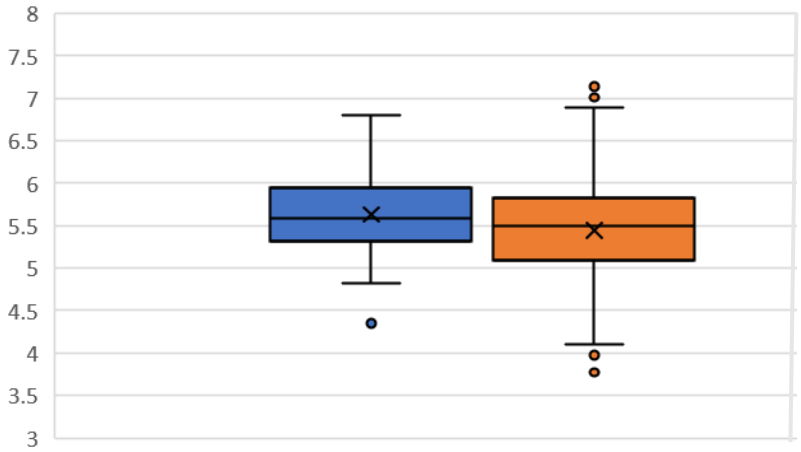

Figure 5: ONSD measurement in different genders. Box and whiskers chart showing the mean (×), median (center line), quartiles (box), minimum and maximum measurements (fences and outliers)

ONSD measurement difference with age

In our study, volunteers aged between 19 and 77 years were examined for ONSD. There was a mild positive correlation between ONSD and age with a Kendall-tau correlation coefficient of 0.048, but this was not statistically significant as the p-value was 0.32 (higher than 0.05).

ONSD measurements in different age groups (divided into decades) are illustrated in figure 6 and table 4. Figure 6 shows ONSD distribution with age. There was no statistically significant difference in ONSD between age groups.

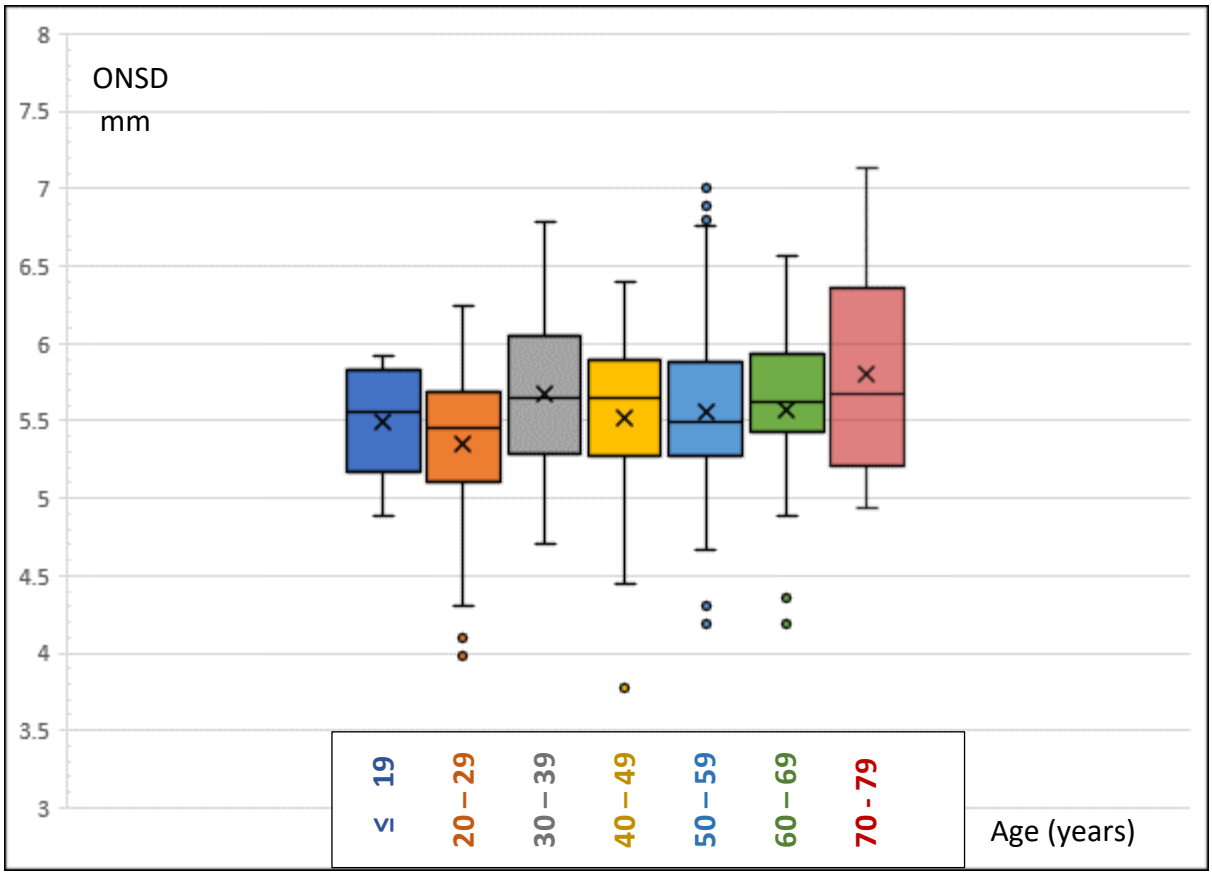

Figure 6: ONSD measurements in different age groups. Box and whiskers chart showing the mean (×), median (center line), quartiles (box), minimum and maximum measurements (fences and outliers).

Table 4: ONSD measurement in different age groups

ONSD (mm)	Age (years) ≤ 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79
Mean	5.49	5.35	5.67	5.52	5.55	5.57	5.80
Median	5.56	5.45	5.64	5.65	5.49	5.62	5.67
Std. Deviation	0.38	0.57	0.52	0.58	0.65	0.57	0.78
95 % percentile *	-	6.21	6.59	6.36	6.79	6.47	-
Minimum	4.88	3.98	4.7	3.78	4.19	4.19	4.94
Maximum	5.92	6.24	6.78	6.40	7.01	6.56	7.13
Number	3	15	16	18	30	13	3
P – value **	0.495						

* 95% percentile not calculated in 1st and last group because of small sample number.
** Kruskal Wallis Test

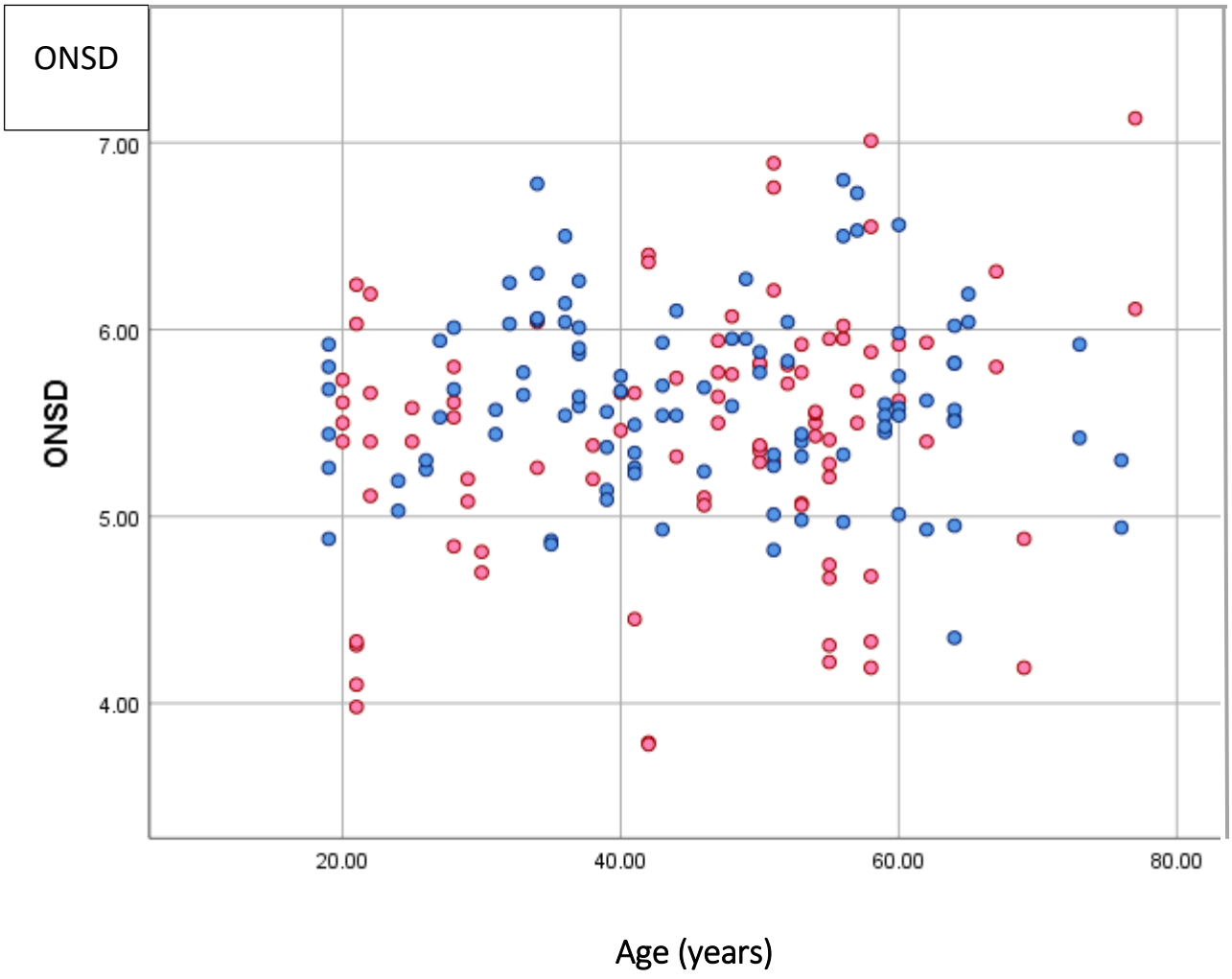

Figure 7: scatter dot chart of ONSD with age and marking for genders.

DISCUSSION

Measurement of optic nerve sheath diameter is potentially a noninvasive simple method to detect raised intracranial pressure as the distention of optic nerve sheath in association with raised ICP have been proved in cadaveric and clinical trials [8,9].

In our study, the mean of normal optic nerve sheath diameter was 5.54mm with upper normal limit of 6.53mm (95% percentile). Similar results are seen in Bauerle et al [17-19] in Germany with a mean ONSD of 5.4mm. Kishk NA et al [20] in Egypt reported a mean ONSD of 5.55mm. Several studies showed a larger optic nerve sheath diameter mean and upper normal limit. In De Masi et al [21] the mean optic nerve sheath diameter was 6.5mm. Lochner P et al [22] showed a mean ONSD of 5.95mm. These two studies reported the highest ONSD, and both are done in Italy. Many other studies showed smaller ONSD. Kim DH et al [23] in Korea showed a mean ONSD of 4.11mm. The lowest mean ONSD measured is by legorova KS et al [24] in Ukraine that reported a mean ONSD of 4.08mm. Difference in examination technique is one reason for this variability in ONSD among studies. Different type of machines and different transducer frequency used in the studies affect obtained image resolution and ONSD measurements. Racial and ethnical differences are factors to be considered in ONSD variation among studies. The optic nerve sheath being a mobile, fluid filled structure is a possible source of this variation.

In this study we did not find a significant correlation between ONSD and age, this is consistent with the studies that measured ONSD in adults. Steinborn et al [25] measured ONSD in children aged 3 months to 17 years using transorbital ultrasound and MRI found a positive correlation between ONSD and age up to 5 years old after which there was no significant increase in ONSD.

Limitations to point in our study is that all examined volunteers are considered to be healthy with normal ICP, since measurement of ICP requires invasive procedures.

Financial support and sponsorship:

Nil.

Conflicts of interest:

There are no conflicts of interest.

CONCLUSION

The mean ONSD measured by transorbital ultrasound was 5.54mm and the upper normal limit was 6.5mm (95% percentile) in a sample of healthy Iraqi population. There is no correlation between ONSD measurements with age or gender.

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